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Primary "Acquired" Hypogammaglobulinemia

Clinical and Genetic Aspects of Nine Cases

By

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Investigations of immunological deficiency diseases originated with Bruton s classical report on agammaglobulinemia (45) and have led to the recognition of different forms of primary hypogammaglobulinemia These have somewhat arbitrarily been divided into 'congenital and acquired cases, depending mainly on the age at onset of symptoms

There is quite good evidence for the existence of a congenital, recessive sex linked hypogammaglobulinemia as shown by pedigrees drawn from published cases (fig 1) (2 22 25 27 30, 31), and also by its occurrence only in male sibs (2 4 13 18 26) Affected male children usually fall ill before the age of one year and though gammaglobulin therapy improves their condition if given early mortality during childhood is high at least in some families

A second group consists of cases in which congenital hypogammaglobulinemia is combined with lymphopenia (23 50) Symptoms occur early in life and in spite of intense treatment the outcome in published cases has been uniformly fatal Affecting sibs of both sexes mostly the offspring of consanguinous parents, this condition is probably inherited as an autosomal recessive trait

The pathogenesis of primary acquired hypogammaglobulinemia, though much discussed is still obscure Earlier investigators postulated an environmental cause of the deficiency Wollheim (61) published an observation of hypogammaglobulinemia in two distantly related women and assumed a genetic basis for the disturbance Fudenberg et al (16) as well as Good et al (17) have published important findings supporting a hypothesis of genetic transmission

Through collaboration of different hospitals in Southern Sweden we were able to collect nine cases of primary adult hypogammaglobulinemia which are presented here, together with pertinent data on the family background

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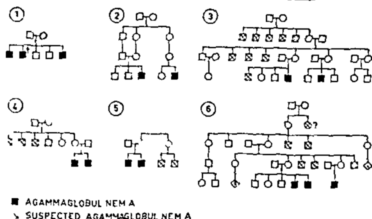


Fig 1 *Pedigrees suggestive of sex linked recessive transmittance of* congenital agammaglobulinemia drawn from published cases
1) Kulneff et al (31)
2) Kulneff (30)
3) Porter (47)
4) Henley (22)
5) Barandun et al (2)
6) Jamieson and Kerr (25)

Material

The material consists of all cases of primary hypogammaglobulinemia in adults observed by the authors All had a distinct isolated hypogammaglobulinemia (table I) observed for at least five years This extended observation precludes the erroneous inclusion of cases of secondary hypogammaglobulinemia as may be seen for example in malignancy All patients experienced *recurrent infections* None showed renal or gastrointestinal protein loss

Also 118 relatives of the nine patients mentioned have been studied for antibody deficiency in their serum

Methods

Paper electrophoretic analysis was performed by the method of C B Laurell et al (38) at the Laboratory of Clinical Chemistry in Malmo (Head Ass Prof C B Laurell) A selection of serologic reactions according to Waldenstrom and Winblad (56) was performed at the Institution of Bacteriology in Malmo (Head Prof S Winblad) Micro immune electrophoreses were done with the method of Scheidegger (52) Semi quantitative determinations of gamma 1A globulin were performed according to a modification (Wollheim) of a method used by Ritzman and Levin (49) on Ouchterlony plates with serial dilutions of test sera The specific antiserum was kindly supplied by Professor C B Laurell Plasma cell counts were made on smears of bone marrow Finally, a genealogic investigation of the nine cases *in the material* was performed

Case reports

Propositus 1 GK (Previously published by Lindholm in 1959) (40) This 28 year old male has a history of recurrent pneumonia on five occasions between age 12 and 21 He also had two episodes of purulent meningitis In 1947 he was admitted to the hospital because of purpura Splenomegaly, hemolytic anemia thrombocytopenia were found WBC *4 100 Lymphocytes 2 000 Blood group* was type O Rh negative and no isohaemagglutinins were detected The purpura disappeared and the haematologic data became normal after splenectomy in 1948 The spleen weighed 1 500 g and its microscopic picture at that time was thought consistent with a Brill Symmer s giant cell lymphoma, however re evaluation of the microscopic sections in 1958 together with a lymph node biopsy showed only non specific inflammatory changes

Hypogammaglobulinemia was diagnosed in 1958 (Lindholm) and he was treated with gammaglobulin since then and has improved considerably After the 5th monthly injection of 24 ml of 12 % gammaglobulin solution the patient experienced nausea and a profuse diaphoresis No loss of consciousness or hypotension occurred A similar reaction recurred 20 minutes after the 36th injection and 20 minutes after the 38th injection he had vomiting diarrhea and chills with a pyrexia of 39 3 C his blood pressure fell from 130 to 90 mm Hg No antibodies against human gammaglobulin were detected (Institution of Bacteriology Lund) Intracutaneous tests with gammaglobulin with and without merthiolate preservative were negative Since 1961

Table I Paper-electrophoretic serum protein pattern

	Total	Albumin	α_1 glob	α_2 glob	β_1 glob	β_2 glob	γ glob
Normal Mean ±2SD (g/100 ml)	6.4–7.8	4.2–5.3	0.23–0.38	0.34–0.59	0.39–0.62	0.24–0.42	0.65–1.10
1 GK	6.6	4.7	0.33	0.64	0.48	0.15	0.31
2 IE	5.9	4.1	0.31	0.69	0.40	0.19	0.21
3 VF	5.5	3.9	0.38	0.55	0.34	0.15	0.17
4 FH	6.1	4.7	0.34	0.47	0.32	0.13	0.16
5 IJ	6.5	4.8	0.34	0.57	0.40	0.19	0.20
6 AP	6.8	5.0	0.42	0.53	0.51	0.15	0.23
7 BB	7.0	5.1	0.43	0.50	0.46	0.19	0.33
8 EL	6.5	4.8	0.32	0.49	0.32	0.21	0.33
9 VS	6.3	4.6	0.36	0.60	0.37	0.11	0.24

such gammaglobulin has been given without adverse reactions. The patient is now in fairly good health and is working full time.

Propositus 2 IE. She is a 45 year-old female who had poliomyelitis in 1924. Repeated respiratory tract infections began in 1933 after a severe pneumonia. Especially after 1949 she was afflicted by chronic productive bronchitis, sinusitis and frequent bouts of long standing pneumonias with varying localisation. Hypogammaglobulinemia was detected in 1956 (Belfrage). The blood eosinophil count was regularly elevated to 900–2 300. Peripheral blood findings were otherwise unremarkable. Lymphocytes 2 300. Slight splenomegaly was present. Sternal puncture showed a plasma-cell count of 1 : 2 000. Lymph node biopsy in 1956 (Prof. Linell) showed large germinal centres with mitoses and an abundance of large reticular cells in the parenchyma. No plasma cells could be detected. The histologic picture was consistent with toxoplasmosis. The Dye test however was judged positive only in a titer of 1 : 50. Her blood group is type A Rh positive and anti B agglutinins are present in a titer of 1 : 1 to 1 : 2. Gammaglobulin administration at regular intervals was started in 1956 and since 1960 she has had continuous treatment with broad spectrum antibiotics. The patient is now in good health working as a children's nurse.

Propositus 3 VF (Identical with case 3 in the publication of Larsson et al. (37).) The patient is a 44 year old woman who has had pernicious anemia since 1943. She has had multiple bouts of pneumonia since 1946 and since 1955 severe bullous emphysema with respiratory insufficiency has been present. She has had chronic otitis and chronic sinusitis for eleven years. A Caldwell Luc operation was performed in 1952. Extreme hypogammaglobulinemia was first detected in 1955 and confirmed in 1957 (Coster). At that time she was started on therapy with 16 ml of 12 % gammaglobulin every second week. Investigation in 1959–60 confirmed true absence of intrinsic factor (37). There was no evidence for a malabsorption syndrome. WBC 8 500. Lymphocytes 2 100. Blood group was type O Rh positive and no isohaemagglutinins were present. 1.3 % plasma cells were found in bone marrow smears. Mild nausea and weakness occurred after a gammaglobulin injection in 1959. In January 1960 she developed severe anaphylactic shock with unconsciousness 5–10 minutes after an injection of gammaglobulin from the same batch which she had previously received without symptoms. Subsequently she showed a positive intracutaneous test with 0.2 ml gammaglobulin. She had no reactions with other batches of gammaglobulin which were administered uneventfully thereafter.

Though never asymptomatic the patient was able to perform light housework until

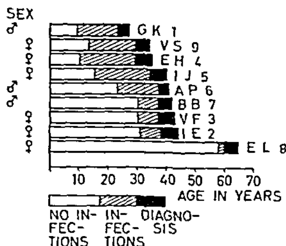


Fig 2 Nine cases of primary acquired hypogammaglobulinemia Sex distribution age at onset of repeated infections and age at which hypogammaglobulinemia was diagnosed

spring 1963, when her condition slowly deteriorated She died in June 1963 with pulmonary insufficiency and right heart failure Partial necropsy revealed right cardiac hypertrophy, pulmonary fibrosis, and hepatosplenomegaly

Propositus 4 EH The patient is a 36 year old woman who had severe pertussis at the age of 6 months and developed chronic otitis at age 7 Since age 12, she has had 30 bouts of pneumonitis as well as chronic sinusitis and a chronic productive cough She had morbilli in 1935, 1939 and 1953 and herpes zoster in 1945 and 1958 A pulmonary resection was performed in 1948 and 1949 because of bronchiectasis Food allergy was evidenced by cutaneous tests against chocolate and egg Extreme hypogammaglobulinemia was detected in 1955 (Belfrage) Blood group was type O, Rh positive, and anti A_1 and anti-A_2 agglutinins were present in a titer of 1 1 Anti B agglutinins were present in a titer of 1 4 Bone marrow puncture showed a plasma cell count of 1 2 000 Gammaglobulin administration of 8 ml 12 % solution twice a month and continuous antibiotic treatment led to a good clinical improvement and no adverse reactions have been seen She works full time although she has moderate pulmonary insufficiency

Propositus 5 IJ The patient is a 41 year-old woman who had scarlatina complicated by repeated bouts of otitis at age 15 Sinusitis began at age 18, and at 20 years she had pleurisy and erythema nodosum In 1944 a diagnosis of pulmonary tuberculosis was made Reactivation occurred in 1949, since therapy in 1949 no further signs of active tuberculosis have appeared She has had at least 5 bouts of non tuberculous pneumonia between 1946 and 1955 and a chronic productive cough since 1953 A Caldwell Luc operation was performed in 1950 because of chronic sinusitis In 1954 she had weight loss, weakness diarrhea, and anemia, Hb 6 4 g%, RBC 1 million, WBC 2,200 A bone marrow examination showed megaloblastic changes for which she was treated with iron and B_1 injections. Three months later she had normal blood morphology In 1956 a diagnosis of extreme hypogammaglobulinemia was made (Kallos) and she was started on 24 ml of 12 % gamma globulin every 3rd week plus almost continuous antibiotic treatment Some clinical improvement has taken place Reexamination in 1959 showed Hb 13 6 g%, RBC 4 8 million WBC 4,600, lymphocytes 1 200 plasma cell count 1 2 000 in a sternal puncture Blood group was type O Rh positive, and no isohaemagglutinins could be found Schilling tests showed 10 and 11 % excretion rising to 13 and 16 % with intrinsic factor supplement these values are not consistent with true pernicious anemia B_1 administration was discontinued in Nov 1961 with no relapse of anemia so far Normocalcemia normal oral glucose tolerance test and absence of steatorrhea are further evidence against a malabsorption syndrome She has for several years experienced some arthralgic pains with morning stiffness and slight capsular swelling of her fingers without functional impairment She remains in fairly good condition

Propositus 6 AP He is a 34 year-old male who has had frequent respiratory tract infections starting in 1944 and at least 20 bouts of pneumonia In 1952 he underwent lobectomy because of bronchiectasis Extreme hypogammaglobulinemia was detected in 1958 (Bjuggren) Since then he has had injections of 16 ml of 12 % gammaglobulin twice a month In 1959 he had meningococcal meningitis Blood group was type O Rh positive and no

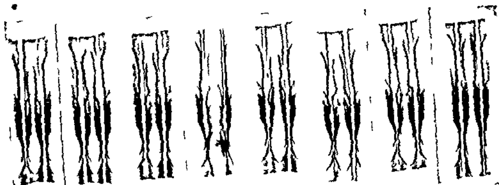


Fig 3 Immuno-electrophoretic patterns of propositi 1–7 and 9 The patient is represented by the middle well on each slide the normal serum by the outer wells A rabbit anti total human antiserum is used

isohaemagglutinins were detected Peripheral blood findings are unremarkable Lymphocytes 2 800 He is now in good condition working as a farmer

Propositus 7 BB He is a 43 year-old male who has had repeated respiratory tract infections since 1950 with at least 5 episodes of pneumonia He has a penicillin allergy (rash) first noted in 1953 with a positive intradermal test in 1954 He had a Caldwell Luc operation in 1957 and the same year he was found to have hypogammaglobulinemia (Coster) and was started on 16 ml of 12 % gammaglobulin a week Blood group is type A Rh positive but anti B is absent Sternal puncture showed complete absence of plasma cells He is still in good health without signs of bronchiectasis WBC 4 300 lymphocytes 1 200

Propositus 8 EI She is a woman born in 1837 who was in good health until 1955 when recurrent purulent respiratory tract infections began She has had sinusitis frequently pneumonitis on at least 5 occasions and a chronic productive cough She developed roentgenologic signs of bronchiectasis Since 1956 she has had recurrent episodes of moderate diarrhea In 1957 she was explored for an anterior mediastinal mass visible on roentgen films since 1948 The tumour was lobulated encapsulated orange sized and solid Microscopic examination showed whirls of elongated cells with fusiform nuclei between which there were lymphocytes and bands of connective tissue Some thymic rests could be seen outside the capsule The diagnosis was thymoma (Ass prof F Bergman) Resistance to infections did not improve post operatively Hypogammaglobulinemia was detected 9 months later in 1957 (Coster) and she has been treated since then with weekly injections of 8–16 ml of 12 % gammaglobulin Laboratory examination in 1960 revealed Hb 13 g% RBC 4 2 million WBC 4 000 lymphocytes 950 serum iron 113 μg% serum B_{12} concentration was normal Schilling test showed 15 % urinary excretion An oral glucose tolerance test was normal as was an upper gastrointestinal series with small intestine films Blood group was type A Rh negative A very weak anti B could be detected with twice the normal amount of serum (Felding) No plasma cells were seen in a bone marrow smear Present clinical condition remains good

Propositus 9 IS She is a woman born in 1928 She was in good health until 1941 when frequent respiratory tract infections commenced Since then she has had at least 12 bouts of pneumonia with chronic bronchitis and recurrent sinusitis Hypogammaglobulinemia was detected in 1957 (Coster and since then she has had replacement therapy with 16 ml of 12 %, gammaglobulin twice a month A sternal puncture showed less than 1 500 plasma cells Lymph node biopsy showed no plasma cells (Prof Ringertz) Blood group was type B Rh negative, and no anti A was present Blood morphology was normal and she has a normal Schilling test Her clinical condition is good

Table II Some clinical and laboratory data

Case	Sex	Blood group	Isoagglutinins		Bone marrow (plasma cells)	Antibody determinations (56)	Splenic enlargement (length > 16 cm)	Biopsy of lymph node
			Anti A	Anti B				
1 GK	♂	0 Rh−	Absent	Absent	—	All reactions negative	Splenectomy in 1948 1 500 g	Absence of plasma cells
2 IL	♀	A Rh+	—	Present	1 2 000	All reactions negative Sabin Feldmann dye test positive 1 50	Slight	Absence of plasma cells
3 VF	♀	0 Rh+	Absent	Absent	1 3%	All reactions negative	Slight	—
4 EH	♀	0 Rh+	Present	Present	1 2,000	Antigammaglobulin border line	Moderate	—
5 IJ	♀	0 Rh+	Absent	Absent	4 2 000	All reactions negative	No	—
6 AP	♂	0 Rh+	Absent	Absent	—	All reactions negative	No	—
7 BB	♂	A Rh+	—	Absent	0 2 000	All reactions negative	No	—
8 FL	♀	A Rh−	—	Weak	0 2 000	All reactions negative	No	—
9 VS	♀	B Rh−	Absent	—	<1 500	—	No	Absence of plasma cells

Further information on the propositi

Fig 2 demonstrates the sex distribution the age at onset of symptoms and the age at which the diagnosis of hypogammaglobulinemia was made in our cases Symptoms i e repeated infections in all but one patient began before age 31 the exception being the woman with a thymoma Table I gives the paper-electrophoretic data gamma and beta₂-globulin distinctly low in all cases Fig 3 shows the immuno electrophoretic patterns In all sera some gamma₂s globulin could be detected by immunologic methods Gamma₁ₓ globulin was extremely low in all our cases as shown with a semi quantitative Ouchterlony plate test Table II summarizes some data also mentioned in the case reports In table III are listed some allergic reactions occurring in our patients

Genealogic findings

Taking advantage of the excellent and reliable church registers available in Swedish parishes, ancestors of all patients have been traced back as far as possible which in many instances was to the latter part of the 17th century Fig 4 a map of Southern Sweden shows the birth places of the grandparents of the propositi One is surprised to find them

Table III Allergic manifestations

Case	Type of reaction
1 GK	Reaction to gammaglobulin injection
2 IE	Loeffler's syndrome? Total eosinophilic counts up to 2 300
3 VF	Reactions to gammaglobulin injections. Positive cutaneous test
4 EH	Food allergy to egg and chocolate
5 IJ	Allergic reaction to autovacc ne injections. Total eosinophilic count of 850
7 BB	Penicillin rash positive skin test in 1954 negative in 1956

mainly in four different areas which are not related to the present living places of the propositi or to the city in which the diagnosis of hypogammaglobulinemia was made. Further investigation proved a direct relationship between cases 1 and 2 (fig 5) who were found to be 5th cousins and between cases 3 and 4 who are 3rd cousins once removed (fig 6) (61). Consanguinity between the parents of case 2 and the paternal grandparents of case 3 is also seen. In fig 7 the pedigrees of cases 5 and 6 are shown. Family links could not be proved but were suspected from the finding of ancestors of both patients in the same isolated parishes. The isolated character of these parishes is expressed by some consanguineous marriages in earlier generations. The pedigrees of cases 7, 8 and 9 do not show any family relations with other cases or ancestral consanguineous marriages in our studies. It is perhaps remarkable however to find 3 cases of hypogammaglobulinemia in an area with a present population of only 30 000.

Efforts were made to find connections between the cases presented here and the two families of congenital sex linked hypogammaglobulinemias studied by Kulneff et al (30 31). These patients live in the Halmstad area (fig 4). No relations could however be proved or even suggested in spite of the tracing of 7 generations of ancestors.

Clinical and laboratory findings within the families

Family I (K (fig 8). The only two sibs of the mother of the propositus died at ages 5 and 7 years. The mother born *in* 1898 developed a hyperchromic anemia in 1954 and was treated until 1960 with liver and intrinsic factor preparations. Anemia relapsed in 1961 and the marrow was megaloblastic. She responded promptly to parenteral B_{12} vitamin therapy and on re-examination in 1963 she showed the following values: Hb 12.5 g%, RBC 3.8 mill/cu, WBC 5 300. Serum B_{12} concentration 130 $\mu\mu$g/ml, a borderline value

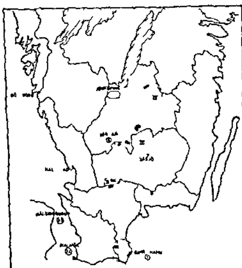


Fig 4 Map of Southern Sweden showing location of the hospitals where diagnosis of hypogammaglobulinemia was established in the propositi (figures 1–9 indicating propositi 1–9). The birthplaces of the grandparents marked ■ are found mainly in areas I to IV. Area I corresponds to ancestors of propositi 1 and 2, area II propositi 3 and 4, area III propositi 5 and 6, area IV propositi 7, 8 and 9.

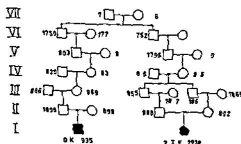


Fig 5 Schematic pedigree of propositi 1 and 2 with birth years of ancestors

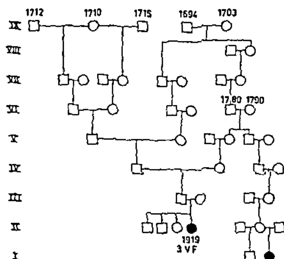


Fig 6 Schematic pedigree of propositi 3 and 4 with birth year of ancestors

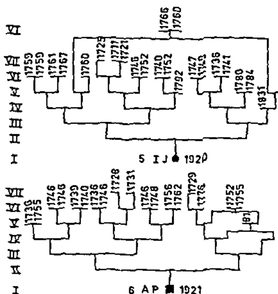


Fig 7 Schematic pedigrees of propositi 5 and 6

(A Killander) Serum folic acid 5 4 $\mu\mu$g/ml, Schilling test showed 2 % urinary excretion without and 6 % excretion with intrinsic factor There was no indication of a malabsorption syndrome Thus she has pernicious anemia refractory to intrinsic factor, perhaps due to previous oral treatment with intrinsic preparations (14) Since 1960 we have observed in her serum a gammass M component with gamma -mobility, the concentration of which slowly increased from 0 9 to 1 9 g% by May 1963 The bone marrow morphology was normal with no increase of plasma cells and no myelomatous bone lesions have been found

One paternal uncle died of well documented gammamyeloma Three of four living uncles had polyclonal hypergammaglobulinemia (Waldenstrom), and two of them were treated for asthma One sister and one brother had also hypergammaglobulinemia of the polyclonal type, but all five sibs remain in good health

Family 2 IE There is pulmonary disease presumed to be tuberculosis among sibs of *the mother, the maternal grandmother, and* the maternal great grandmother Paper electrophoresis performed on the sera of 5 living relatives is normal

Family 3 VT (fig 9) Pernicious anemia occurs in two paternal aunts and one paternal first cousin Polyclonal hypergammaglobulinemia has been found in one sister two paternal cousins, and though less pronounced, in three of six second cousins One nephew had a slight hypergammaglobulinemia for his age and a low concentration of gamma$_{1A}$ globulin Both a male first cousin and a male first cousin

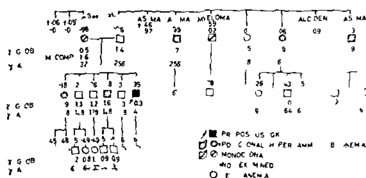


Fig 8 Family 1 GK Gammaglobulin measured as g% of gammaglobulin on paper electrophoresis Gamma$_{1A}$ globulin measured as last dilution giving detectable gamma$_{1A}$ line with specific anti gamma$_{1A}$ globulin on Ouchterlony plates Normal value remains positive at more than 1 32 dilution

once removed have been treated for thyrotoxi cos s The two ch ldren of the propos tus have normal immunoglobul ns

Far ly 4 EH (f g 10) The pat ent s mother d ed at age 51 of non tuberculous Add son s d sease The father is n good health but re fused to cooperate in our stud es A paternal aunt is sa d to have suffered from many in fect ons to wh ch she succumbed dur ng adolescence The pat ent s f rst ch ld a son born n 1953 has a border l ne low gamma globul n con entrat on (0 59 g%) as assessed by paper electrophoresis and an abnormally low gamma A globul n concentrat on Her second ch ld a daughter d ed dur ng the neonatal period after an operation for atres a of the esophagus The th rd ch ld a bo was born in 1959 w h extreme hypogamma globul nem a (0 14 g%) The mother (EH) at parturit on had a gammaglobul n con entrat on of 0 20 g% At age 4 the ch ld st ll has low concentrat on of whole gamma 0 36 g%) and gamma A globul ns Ne ther ch ld has had any increased tendency toward nfect ons

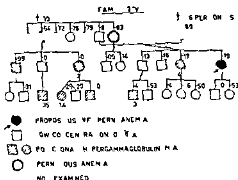
Fam ly 5 IJ (f g 11 One paternal uncle has polyclonal hypergammaglobul nem a A paternal aunt has cr ppl ng rheumato d arthr t A male nephew aged 4 has low concen trat ons of mmuno globul ns but no d spos t on for nfect ons

Fam ly 6 1P (f g 12 Two of the pat ent s s bs d ed of mal gnant d sease One s ster ha polyclonal hypergammaglobul nem a Two nephews had normal ga nmass bu lo v gammaA glob l n

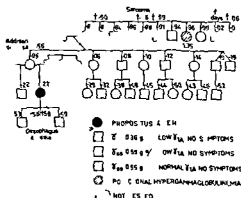
Fam l e an l 8 were not nvest gated

Fam ly 9 I S (g 13 The pat ent s mo her and older ch ld ha l low gammaA globul n co centrat ons No o her al ormal ty as bserved

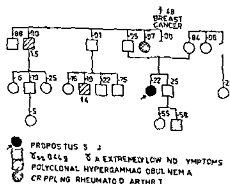
Thus as shown in fig 14 an abundance of polyclonal hypergammaglobul nem a was found in families 1 and 3 and to a less degree in famil es 5 and 6 Family 1 was uniq ie in showing also individuals with monoclonal hypergammaglobul n



F g 9 Fam ly 3 VF F gures below hatched sym bols ind cate paper electrophoret c gammaglobul n value



F g 10 Fam ly 4 EH



F g 11 Fam ly 5 IJ

emia Seven individuals in families 3 4 5 6 and 9 showed decrease in one or more immunoglobulin fractions witho t any disposition for infections

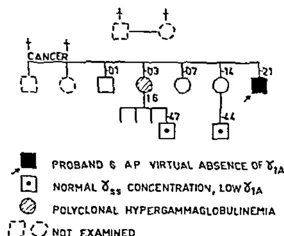


Fig 12 Family 6 AP

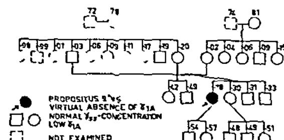


Fig 13 Family 9 VS

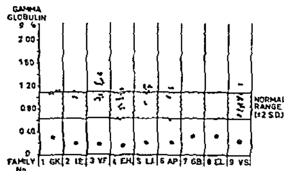


Fig 14 Gammaglobulin values as measured paper electrophoretically of 9 propositi ○ and relatives of 7 of them

Serological examination for a variety of antibodies (56) revealed negative Wassermann s, Meinicke s and Kline's reactions in all individuals except the parents of case 1, in whom positive TPI-tests established the suspected diagnosis of acquired syphilis The gonococcus complement-fixation test was negative in all instances but one, the younger son of the oldest brother of propositus 3 Anti streptolysin and antistaphylolysin titrations were frequently found elevated, as they are known to be in the general population

Rose-Waaler's reaction was strongly positive in one member of family 5 (fig 11), a 65-year-old woman with crippling rheumatoid arthritis, but negative in all other sera Thus, we were not able to find an increased occurrence of the R A S-factor among the relatives of adult hypogammaglobulinemia patients

We have not found any living relatives with increased disposition for infectious diseases

Discussion

Though it is known that contact with foreign protein during postnatal life is the inciting agent for immunoglobulin production, and though infectious diseases (6) as well as endocrine disorders (36) influence the levels of immunoglobulins in the serum, the fundamental mechanism by which they are kept constant in a population remains unknown Primary hypogammaglobulinemia is regarded as a condition with a marked failure to synthesize antibodies without any other apparent primary disorder such as invasion or depression of bone marrow or lymphoid system by malignant disease, and without abnormal protein losses secondary to gastrointestinal tract or renal disease All nine cases presented here must therefore be classified as true primary hypogammaglobulinemia

Despite the extensive interest in primary hypogammaglobulinemia with signs of immunological paralysis in adults it remains a rare disease In the United Kingdom a Medical Research Council working group is trying to estimate the fre-

quency of this disease, and has found about 12 new cases of hypogammaglobulinemia each year since 1956 (54) Two-fifths of these are in adults However inadvertent inclusion of some secondary cases and some transient physiologic conditions was recognized The sex ratio among the adults was 10 males 22 females and was similar to that in the present study 3 males 6 females Barandun et al (2) reviewed published cases together with their own material, and found 18 in males 13 in females, so that a pronounced sex difference is not apparent

A few cases are recorded of familial occurrence of disease states which possibly might have been primary hypogammaglobulinemia Homburger and Petermann (24) published a family with idiopathic dysproteinemia , in which generalized edema and leg ulcers were prominent features One female, age 51, also had a history of frequent infections and low albumin and gammaglobulin levels Her capacity to produce antibodies was reduced A brother of hers had a low level of gammaglobulin in his serum and frequent infections This family could represent some more profound defect in amino acid metabolism as suggested by Waldenstrom (55) Schick and Greenbaum (53) described a similar syndrome without liability to infections in a 12 year old girl and her mother Kushner et al (32) observed a family where leukopenia splenomegaly antibody deficiency syndrome and moderate hypogammaglobulinemia occurred in an adult male and in three of his seven children of both sexes Brehm and Morton 9) observed two brothers with hypogammaglobulinemia and lymphatic leukemia Excepting only the Kushner family none of these cases seem to fulfill the criteria of clearcut primary hypogammaglobulinemia Apart from this family we have not been able to find in the literature previous to the preliminary report by one of us (61), statements on the familial occurrence of adult hypogammaglobulinemia That the condition generally has been described as sporadic should not however, be interpreted as excluding inheritance, as discussed in a paper by Klunker and Schnyder (29)

In addition to the 2 pairs of patients (cases 1 GK and 2 IE, 3 VF and 4 EH) who share a common ancestry suggesting a genetic basis for this syndrome, the children of propositus 4 EH are of interest especially the youngest one That boy had congenital hypogammaglobulinemia similar to that of newborn children of hypogammaglobulinemic mothers reported by Good and Zak (21) and by Lindell (39) But, in contrast to what happened with them this boy increased his gammaglobulin during infancy only slowly and still at the age of 4 years has abnormally low values for the gammaglobulin fraction as a whole, and for the gamma$_{1A}$-globulin Also his older brother has value somewhat low for his age Both children have been in a fairly good health without frequent infections but their future course will be of great interest

There are not many reports on consanguinity among parents of adults with hypogammaglobulinemia, but Bouton et al (8) described a girl aged 17, the father of whom was the offspring of related parents This is similar to our cases 3 VF and 6 AP The parents of our cases 2 IE and 5 IJ were first and third cousins respectively (figs 6 and 7), but the significance of this is not clear

Lindell (39) briefly described two cases of hypogammaglobulinemia in adults

whose relatives had border-line low gammaglobulin values It would be worth while to reinvestigate these families with immunologic quantitation of the gamma-globulins

A genetic concept of benign polyclonal hypergammaglobulinemia seems well established (35) The occurrence of this condition among the relatives of four of the present propositi is in accordance with previous papers by Young et al (62), Good and Zak (21), Citron (10), Zelman and Levin (63), Lindholm (40), and others Connective tissue diseases such as collagen diseases, including rheumatoid arthritis, have been described with high frequency both in patients with hypogammaglobulinemia (20, 28) and in the families of probands with primary "acquired" hypogammaglobulinemia (15, 17, 58) A family studied very thoroughly by Wolf et al (59, 60) illustrates this feature The proband is a 33-year old female with hypogammaglobulinemia and rheumatoid arthritis, with negative rheumatoid factor activity Other family members are afflicted with SLE arthritis idiopathic thrombocytopenia, thymoma, leukemia, etc Serum analysis of family members revealed both hyper- and hypogammaglobulinemia, anti nuclear factor occurrence, and isolated reductions in $gamma_{1A}$ and $gamma_{1M}$-globulins

Laplane et al (34) studied the family of a 12-year-old girl with atypical' agammaglobulinemia with a lack in $gamma_{SS}$- and $gamma_{1A}$ globulins but elevated $gamma_{1M}$-globulin Both parents were normal but in the sera of two brothers no $gamma_{1A}$ globulin could be detected Fudenberg et al (15) found a high incidence of rheumatoid agglutinating activity in parents and siblings as well as elevated gammaglobulin levels Fudenberg et al (16) present results of gamma$_{SS}$-, $gamma_{1A}$-and $gamma_{1M}$-quantitations in 6 families, in three of which there were cases of classical congenital hypogammaglobulinemia and in three of which cases of "acquired" hypogammaglobulinemia In the first group the propositi generally lacked all three kinds of immunoglobulins while their parents generally were normal In the second group as many patterns were found as families studied The authors suggest an attractive hypothesis for the genetic control of immunoglobulin synthesis, according to which four different loci control four different subunits Our data on family 9 VS could lend support to this hypothesis One should not, however, draw too wide conclusions from such observations, because West et al (57) found a wide individual variation in $gamma_{1A}$- and $gamma_{1M}$-globulin concentration They collected 13 children, up to 11 years old, with isolated $gamma_{1A}$ globulin deficiency who had varying diseases and no immuno-paralysis So this condition might be not too rare and by no means confined to families with hypogammaglobulinemia

It is well known from previous studies (46) that allergic reactions can take place in hypogammaglobulinemia, perhaps the most dangerous being anaphylactic shock after gammaglobulin injections This complication was reported in the United Kingdom ten times in 6 individuals among 82 patients with hypogammaglobulinemia who got more than 10 000 injections in toto Most reactions were not severe (54) Barandun (3) could regularly produce anaphylactic reactions in certain individuals by intravenous administration of gammaglobulin solutions under standardized conditions These reactors were much more common among hypogammaglobulinemia patients

The effect seemed also to be coupled to the anticomplementary activity of the gammaglobulin administered and pepsin digested gammaglobulin could be given without adverse effects In our cases two of the nine patients reacted to gammaglobulin on five occasions In case 1 GK it is not quite clear what caused the reaction, while we have reason to believe that case 3 VF had been sensitized to a certain batch of gammaglobulin

Penicillin sensitivity is repeatedly reported in hypogammaglobulinemia though the reactions in general seem to have been mild ones (11 27, 43) Good et al (18) describe a patient with a known food allergy to fish which disappeared after the onset of hypogammaglobulinemia The same authors have found atopic eczema in some boys with congenital agammaglobulinemia, but they have not been able to demonstrate the causative antigen Larsson et al (37) described a successful desensitization in a hypogammaglobulinemia patient allergic to merthiolate It must be concluded that some antibody producing capacity is retained by these patients, though not sufficient for protective purpose, this view is also supported by the studies of MacCallum (41) and Baron et al (5)

The coexistence of thymoma and adult hypogammaglobulinemia has been noted in 7 previously reported instances (19, 33, 42 44, 48 51) our case 8 EL is thus the eighth reported We agree with Good that this must be more than mere chance It is striking that these patients have been elderly with a mean age of 55 years Thymectomy has in no case relieved the immunological paralysis and does not seem indicated if malignancy is excluded Neonatal thymectomy in laboratory animals results in impaired antibody synthesis (12) and these experiments indicate that the thymus has a leading role in the development of the peripheral lymphatic system This field has been recently reviewed (1)

Though many authors now regard primary acquired hypogammaglobulinemia as an inherited trait, the mode of transmission remains obscure The family relations found between cases 1 GK and 2 IE and between cases 3 VF and 4 FH are consistent with an autosomal inheritance It is possible that some unknown trigger mechanism is necessary for the precipitation of the disease In the present study the 21 living sibs did not show antibody deficiency and there was no history of frequent infections among the deceased sibs most of whom died of malignant and cardiovascular diseases

Summary

Nine cases of primary 'acquired hypogammaglobulinemia are presented with pertinent clinical and immunologic features Thymoma was found in one case Allergic manifestations e g in response to gammaglobulin administration were seen in several cases A child of a hypogammaglobulinemic mother had congenital hypogammaglobulinemia which has not regressed in the expected way, but is still present at age 4 years Family studies showed other immunological abnormalities in most families Genealogic studies proved a relationship between two pairs of patients Two further patients came from the same isolated parish and the remaining three also came from a district in common These observations lend further support to a genetic basis for the disease

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Addendum

During the course of printing this paper, J H Rockey et al (J Lab clin Med *63* 205 1964) have reported the isolated absence of gamma$_{1A}$ globulin in two healthy physicians Further R A Good and R D A Peterson (personal communication 1964) have observed a case a 62 year-old male with hypogammaglobulinemia in whom the thymoma was a surprising post mortem finding and S Godfrey (Brit Med J *i* 1159 1964) has described a case of thymoma with hypogammaglobulinemia in an identical twin, a 63 year old woman

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Isotope Nephrography with ^{131}I "Hippuran"

I Technique and Experience in Various Medical Renal Diseases

By

A R Krogsgaard and Th Friis

That a relationship exists between unilateral renal disease and hypertension has been known for the past 25 years Butler (2) in 1937 was the first to report a case of unilateral pyelonephritis with hypertension in which nephrectomy normalized the blood pressure Later a number of authors including some from Scandinavia (1 4, 10 11 14a 15 23) published reports of similar operations For a time, there was considerable optimism in respect to the possibilities of curing so-called urological hypertension in which the underlying unilateral renal disease was usually found to be contracting pyelonephritis hydronephrosis with atrophy and congenital hypoplasia more rarely tuberculosis or renal infarcts Extended experience however gave rise to some pessimism as permanent cure following nephrectomy proved to be far more uncommon than originally assumed This has been emphasized particularly by Smith (16) whose critical review of 242 cases of nephrectomy performed because of urological hypertension revealed a definite cure in less than 20 %

Interest in this problem was revived, however, when the advent of arteriographic technique showed that some hypertensive patients had abnormalities in the vascular supply to the kidney These problems will be discussed in a subsequent communication (5) Here it will merely be stated that to day there is an increasing necessity for subjecting hypertensive patients to investigations for unilateral disease of the kidney and in particular its vascular supply It is impracticable to perform renal angiography on all patients, so the suspicious cases have to be picked out by various preliminary investigations Guidance is obtained primarily from the history and the intravenous pyelography In order to confirm unilateral renal ischaemia Howard *et al* (6) introduced the split function test comprising a separate study of the function of each kidney based upon the fact that an ischaemic kidney re absorbs more water and sodium than normal However, this latter procedure demands bilateral ureteral catheterization it is technically difficult and a great strain on the patient so that

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it is unsuited for extensive use Since, moreover, intravenous pyelography and its technical variants, including nephrotomography, seriography, and investigation during forced diuresis may be normal even despite arterial stenosis, there is a need for supplementary diagnostic procedures, especially those which are applicable as screening tests

The German workers Oeser and Billion (14) used a radioactive dye in studying renal function, but they measured the activity in the collected urine Actual isotope nephrography was, in fact, not introduced until Taplin et al (20), after intravenous injection of ^{131}I-diodrast, measured the activity in each renal area separately Winter (24, 25, 26) has elaborated this method Since, however, diodrast is also concentrated in the liver, there will be an extra-renal increased radiation over the right kidney, so a search was made for other substances taken up selectively by the kidneys This requirement is fulfilled by various compounds, such as Urokon, Miokon, Hypaque, and Renografin, but their excretion is so slow that the test period is too long for practical purposes

Nordyke et al (13) introduced the sodium salt of orthoiodo-hippuric acid ("Hippuran") in nephrography The excretion of this substance is not only selective in the kidney, but it is also so rapid that the test period need be only 15—30 min Ever since, ^{131}I-labelled Hippuran has been the drug of choice Magnusson (9) has studied the distribution and fate of Hippuran in the body

Methods

During the investigation the patient lay prone, with a cylindrical cushion under his abdomen — in an attempt to fix the kidneys ^{131}I Hippuran (Philips, Amsterdam Its specific activity is about 200 μC/mg) was injected intravenously in a dosage of about 30 μC (which is a radiation dose considerably below that in pyelography) The dosage was determined by counting over the syringe before and after the injection, at the same distance as over the patient The activity was recorded over the kidney, for 30 min after the injection, by means of a $1^1/_2$ inch NaI thallium activated scintillation crystal detector screened with lead and an appurtenant pulse height analyzer, scaler, ratemeter (Tracer lab) and recorder (Philips) Counts are recorded on the scaler every 2 minutes The chart of the recorder is $^1/_2$ cm/min Maximum deflection= 3,000 cpm The distance from the skin to the crystal was 15 cm the aperture of the collimator 7 cm in diameter and the angle 12° The distance of the collimator from the skin is 5 cm These technical data correspond to what Nordyke and Tonchen (12) have reported as being optimal on the basis of their systematic studies on the influence of technical factors upon the accuracy and reproducibility of the method These authors pointed out that previously the distance had often been too short and the collimation too narrow This increases the inaccuracy, as the counts are then made only over a limited area of the kidney

The adjustment of the crystal over the kidney was based on preceding intravenous pyelography Since the latter is done in the horizontal position, we preferred using the horizontal position in the nephrography also Incidentally, this eliminates the possibility of a descent of the kidney It must be mentioned, however, that we investigated the patients prone, while the pyelography was done supine

Since we do not yet possess a double unit, we had to study each kidney separately on two consecutive days This, of course, involves the possibility that the renal function has not been exactly identical on these two days, especially because of a variation in hydration which is known to be able to influence the result (13, 21), but less so with Hippuran than with diodrast According to Wedeen et al (22), however, the differences in urine flow must be very considerable before they give rise to definite alterations in the nephrogram In order to detect the significance of this factor we measured the activity in urine voided 40 min after the injection as well as the urinary output (1—3 ml/min) We found only

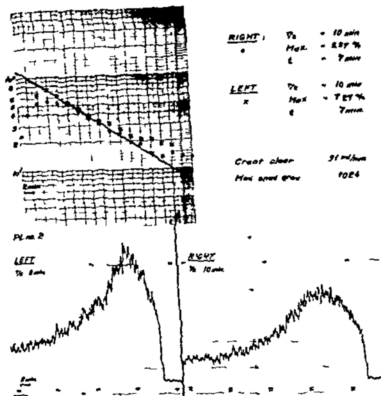


Fig 1 Normal nephrogram (case 2 table I) For abbreviations cf table I The curves in the upper left hand corner represent the values in a semilogarithmic system At the bottom the curves traced by the recorder to be read from right to left

slight day to-day variations indicating that renal function has been relatively constant The patients were investigated at the same time of the day at 1—2 p m

Results

We shall first describe the normal nephrogram (fig 1) and its interpretation

In the original papers Winter (24) and Taplin et al (20) described 3 phases

1 A rapid ascending so-called vascular phase, said to represent the blood flow

2 A secondary somewhat slower rise reaching a maximum in 3—5 min, said to represent tubular function

3 The descending phase, said to represent excretion in and flow from the pelvis

We shall later return to the functional significance of these phases

In assessing our curves we used the following parameters

1 Time from injection to attainment of maximum value (t)

2 Maximum value expressed as a percentage of dosage (Max)

3 Half life T/2 for phase 3

The latter was measured partly directly on the curves traced by the recorder and partly computed from a curve plotted in a semilogarithmic system which makes the decrease approximately rectilinear

Table I. Renal function and nephrography in 10 normal subjects

Case no	Sex	Age	B P	Serum creatinine (<1.3 mg/100 ml)	Creatinine clearance (>67 ml/min)	Max. conc. ability (>1,022)	T/2 measured (<20 min)		T/2 computed (<20 min)		Max (>2.0%)		t (<7 min)		U (>45%)	
							Left	Right	Left	Right	Left	Right	Left	Right		
2	♂	56	125/80	1.0	91	1.024	8	10	10	10	7.3	5.6	7	7	—	—
35	♂	54	140/100	1.2	81	1,026	10	10	12	14	3.4	5.7	5	5	67	43
36	♂	58	130/80	1.1	93	1.022	6	7	4	5	4.6	2.7	3	5	59	62
58	♀	72	140/90	0.9	85	1,024	7	5	7	8	6.5	5.8	5	3	68	—
66	♀	53	150/90	1.1	60	1,026	14	18	14	22	4.8	7.9	7	9	43	—
67	♂	64	120/80	1.0	63	1,023	—	—	6	8	*5.2*	*2.5*	3	3	62	66
69	♂	54	160/80	1.3	63	—	14	16	14	18	8.9	6.3	13	7	51	54
70	♂	39	135/85	1.2	85	1,024	9	8	9	9	6.2	5.5	7	7	83	85
79	♀	44	110/70	1.1	72	1,022	10	6	11	7	5.0	3.7	7	5	64	75
81	♀	47	115/75	1.0	72	1.022	6	10	6	6	8.1	8.9	9	7	51	—

T/2 measured = Time from maximum value to half this value has been reached on the descending phase, measured on the curve traced by the recorder
T/2 computed = Half life in a semilogarithmic system for the descending phase
Max = Maximum value over the kidney as % of dose
t = Time from injection until the maximum value over the kidney has been attained
U = Urinary excretion of radioactivity as % of dose 40 min after the injection

Creatinine clearance converted to 1.73 sqm body surface
The italicized numbers indicate disparity between the two sides

These half lives, the measured and the computed, afforded in the majority of our cases consistent data regarding renal function. However, the computed T/2 appeared *in some cases to accord better with* the other findings. In the event of a greatly prolonged T/2 the experimental period did not permit an accurate determination of the directly measured half life (in which case it was stated as infinite). In these instances a more exact value could be obtained in the semilogarithmic system.

Our normal series consists of 10 patients (table I) with normal blood pressure, serum creatinine, endogenous creatinine clearance (in 3, however, at the lower limit of normal), concentration test and pyelographic appearances. From these findings we felt justified in concluding that the *normal values* in the present technique were T/2 < 20 min, maximum value > 2 % and t < 7 min. *Incidentally, it will be seen that the maximum* value is the parameter which showed most marked disparity between the two kidneys. These normal values are in keeping with those found by Stewart and Haynie (18).

In 5 cases we repeated the investigation on the same side in order to gain an impression of the *reproducibility of the curves*. The repeated studies showed an acceptable conformity, especially in respect to T/2 (table II).

In addition to the normal values for the above parameters the criteria of a disparity in the function of the two kidneys

Table II Results of repeated isotope nephrography on the same side in 5 patients For abbreviations, cf table I

Case no	Sex	Age	B P	Eye ground	Serum creatinine (< 1 3 mg/100 ml)	Creatinine clearance (> 67 ml/min)	Max conc ability (> 1 022)	T/2 measured (<20 min)	T/2 computed (<20 min)	Max (> 2 0 %)	t (<7 min)	U (> 45 %)
42 I	♂	38	180/110	I	0 9	86	1 020	8	6	8 2	7	70
II								8	7	5 9	5	51
47 I	♂	61	160/90	I	1 1	74	1 022	10	74	1 7	3	20
II								9	44	2 4	5	16
45 I	♂	54	130/90	Nat	1 1	70	1 009	8	17	4 1	5	54
II								6	12	5 4	5	50
53 I	♂	68	150/80	Nat	1 0	86	1 020	28	16	4 7	7	27
II								20	16	6 8	9	32
2 I	♂	56	125/80	Nat	1 0	91	1 024	8	10	7 3	7	—
II								—	10	7 3	7	—

must be considered On the basis of the normal series and of the group of patients with various uni and bilateral renal diseases we take a *disparity between the two kidneys* to be present when one of the parameters is one half of (Max value) or twice (t and T/2) the other side, or when more than one parameter shows a less marked disparity but in the same direction

Our *material* comprises 85 investigations on 68 patients In addition to the above mentioned normal group of 10 persons we studied 26 patients with arterial hypertension — who will be described in a subsequent paper which deals particularly with renal artery stenosis (5) In the present paper we have tried to assess nephrography in relation to other renal function tests by studying also 16 patients having chronic pyelonephritis and a mixed group of 16 patients with various renal disorders The results are given in tables III and IV

A The nephrogram as an indication of renal parenchymal disease and its relationship to other renal function tests

The various renal diseases manifested themselves distinctly in the nephrographic findings A typical example of the nephrographic appearances in impaired renal function is case 19 (table III) who suffered from chronic pyelonephritis The nephrogram is shown in fig 2 It has a low and flat curve i e a small max value and a prolonged T/2 whereas t is normal In our studies this type of nephrographic change proved to occur quite uniformly in the various medical renal diseases with functional impairment be it hypertensive nephrosclerosis pyelonephritis or chronic glomerulonephritis

We investigated whether the nephrogram could be related to the conventional tests of renal function Our findings were as follows

Table III Renal function and nephrography in 16 patients with chronic pyelonephritis For abbreviations, cf table I

Case no	Sex	Age	B P	Eye ground	Serum creatinine (<1 3 mg/100 ml)	Creatinine clearance (>67 ml/min)	Max conc ability (>1 022)	T/2 measured (<20 min)		T/2 computed (<20 min)		Max (>2 0 %)		t (<7 min)		U (>45 %)	
								Left	Right	Left	Right	Left	Right	Left	Right		
* 1	♂	32	180/80	Nat	1 3	52	1,028	—	—	18	24	*4 6*	*1 6*	5	5	—	—
*12	♀	45	150/90	Nat	1 5	55	1,018	*10*	*26*	22	22	2 6	2 1	3	3	—	—
16	♀	60	180/130	II	4 4	16	1 012	∞	∞	∞	*68*	*0.5*	*1 3*	*25*	*5*	—	—
20	♀	54	170/100	I	6 1	8	1 013	∞	∞	150	150	2 0	2 6	9	5	5	—
23	♀	54	125/80	Nat	1 5	40	1 022	∞	∞	*170*	*76*	2 7	3 5	7	13	22	—
29	♀	70	130/80	Nat	3 6	22	1 010	*60*	*28*	*136*	*68*	2 1	2 1	5	5	16	6
47	♂	61	160/90	Nat	1 1	74	1,022	20	18	30	26	1 7	1 2	3	3	16	11
56	♀	45	120/80	Nat	1 0	63	1,016	8	14	8	9	9.2	9 3	5	5	61	56
*17 I	♀	41	125/80	Nat	1 7	68	—	*27*	∞	43	72	4 6	4 9	9	9	—	—
II					1 5	39	1 009	*34*	∞	*37*	∞	*3.2*	*6.9*	11	13	—	—
**19 I	♀	67	210/100	I	2 9	21	1 010	∞	∞	116	62	1 7	1 7	*11*	*5*	—	—
II					2 9	17	1 012	*40*	*20*	*116*	*40*	2 8	2 2	9	7	—	—
*14 I	♂	43	150/80	Nat	2 9	24	1 005	24	38	49	70	*3 1*	*1.5*	19	11	—	—
II					2 9	23	1,008	∞	∞	38	38	2 6	3.2	17	15	—	—
**26 I	♀	33	160/100	Nat	1 6	65	1 012	20	14	19	22	4 0	3 5	7	7	40	36
II					1 9	59	1 016	∞	∞	58	66	4 0	2 4	*3*	*11*	36	29
III					—	—	—	30	24	27	25	2 3	2 8	7	5	49	48
43 I	♀	36	120/105	Nat	1 5	31	1 011	26	—	38	36	4 1	2.5	5	7	42	37
II					1 6	30	1 011	36	24	36	24	2.2	3 7	*3*	5	34	39
48 I	♀	58	150/90	Nat	1 6	59	1,020	28	28	31	32	4 8	9.2	*5*	*11*	38	40
II					1 4	57	1 018	*32*	*14*	30	21	3 6	4 4	14	15	32	38
52 I	♀	65	180/110	I	1 3	48	1 022	22	*15*	22	*26*	1 6	3 1	3	3	55	39
II					1 3	51	1 013	18	22	22	25	3 1	3 0	3	3	40	52
62 I	♀	65	170/110	II	1 4	51	1 018	16	24	16	18	2 6	3 4	3	3	48	59
II					1 3	37	1 016	*18*	*7*	20	11	3 7	4 1	*7*	*3*	32	15

* Right sided papillary necrosis
** Left sided papillary necrosis
I II, and III indicate before during and after administration of phenacetin 3 g daily for 10 days
The italicized numbers indicate disparity between the two sides.
Case 23 had left sided pelvic calculi

1 There is an obvious negative correlation between T/2 and the creatinine clearance (fig 3)

2 There is also a negative correlation between T/2 and the renal concentration power (fig 4), but not quite so marked

3 There is a positive correlation between the max value and the creatinine clearance (fig 5)

Table IV Renal function and nephrography in 16 patients with various renal diseases For abbreviations, cf table I

Case no	Sex	Age	Diagnosis	B P	Eye ground	Serum creatinine (<1 3 mg/100 ml)	Creatinine clearance (>67 ml/min)	Max conc ability (>1 022)	T/2 measured (<20 min)		T/2 computed (>20 min)		Max (>2 0 %)		t (<7 min)		U (>45 %)	
									Left	Right	Left	Right	Left	Right	Left	Right		
11	♀	68	R. nephrectomy	160/80	Nat	1 4	61	1 020	—	—	51	87	*4.0*	*1.3*	5	3	60	52
27	♀	67	R. nephrectomy	180/110	Nat.	1 9	36	1 021	*13*	∞	*13*	∞	*4 0*	*1 4*	7	3	24	—
28	♀	68	R nephrectomy	170/90	II	1 6	36	1 024	*10*	∞	*18*	*62*	*4.2*	*1 0*	5	7	31	34
7	♂	15	Ac gl nephritis	130/80	Nat	1 1	82	1 021	16	—	19	—	5 0	—	5	—	—	—
33	♂	19	Ac. gl nephritis	140/70	Nat	1 1	100	1 020	2	*12*	2	*10*	3 0	4 0	9	9	65	70
59	♂	30	Ac gl nephritis	130/90	Nat	1 1	118	1 030	8	6	8	6	7.3	5 0	7	5	41	39
15	♂	24	Chr gl nephritis	220/140	IV	1 9	39	1 017	∞	∞	39	41	1 4	0.8	5	7	26	30
13	♀	49	R. hydronephr	190/120	I	1 0	72	1 018	*25*	∞	*18*	∞	6 7	3 4	*15*	*38*	44	—
24	♂	48	Amyloid kidney	125/80	Nat	1 4	57	1 022	6	10	16	16	4.5	5 1	3	5	49	49
34	♂	59	Hyperparathyr	120/60	Nat	1 4	49	1 014	∞	∞	36	52	2.9	4.2	15	17	23	27
45	♂	44	Hypercalciuria	130/90	Nat	1 1	70	1 009	6	8	12	17	5 4	4 1	5	5	50	54
37	♂	62	*Prost hyp*	120/80	Nat	1 0	66	1 018	6	7	13	22	4 3	6 6	3	5	32	32
53	♂	68	Prost hyp	150/80	Nat	1 0	86	1 020	20	28	16	16	6 8	4 7	9	7	32	27
38	♂	30	Albuminuria	130/80	Nat	0 9	119	1 030	12	16	12	22	2.2	1 3	5	5	51	62
51	♂	67	Tum of r kidney	120/100	Nat	1 2	54	—	*18*	∞	*18*	∞	3.8	2 0	5	*19*	66	*42*
74	♀	62	Tum of l kidney	140/100	Nat	1.2	60	1 022	*56*	*18*	*44*	*18*	*1.9*	*7.9*	5	5	43	45

The italicized numbers indicate disparity between the two sides

4 On the other hand there is no relationship between t and the creatinine clearance

As stated above, we determined the activity in the urine voided in the first 40 minutes after the injection (U) There proved to be a distinctly negative correlation between U and T/2 (fig 6) whereas *no relationship was found between U* and the creatinine clearance or the max specific gravity of the urine

From what has been stated above it may be seen that isotope nephrography reflects renal function in various ways, and this we tried to utilize

Among the patients with pyelonephritis there were several with phenacetin abuse In 8 of these patients we investigated whether nephrography, carried out before and 10 days after administration of phenacetin (1 g three times daily), could demonstrate an alteration in renal function The result is shown in the lower half of table III Only case 26 showed a distinct alteration in the nephrogram during the phenacetin tolerance test, the parameters being distinctly deteriorated in order to improve again after the end of the phenacetin test The explanation why other patients did not also show an effect upon renal function may be that these patients have not been sensitized to phenacetin or that the phenacetin tolerance test was too short lasting

Fig. 2. Nephrogram in a case of chronic pyelonephritis, uraemia and left sided papillary necrosis (case 19, table III). For abbreviations cf. table I.

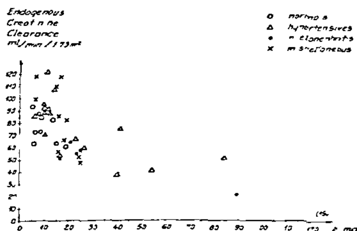


Fig. 3. Relationship between half life in the descending phase of the nephrogram (T/2 computed) and endogenous 24 hour creatinine clearance. The figure includes only patients without a disparity between the two sides and T/2 calculated represents the mean value for the two sides.

B. Disparity between right and left nephrogram

Assessed on the basis of the named criteria there was a disparity between the function of the two kidneys in 27 of the 68 subjects. Table V shows the underlying disease among these patients. Among the hypertensive subjects there was a disparity in the presence of renal artery stenosis

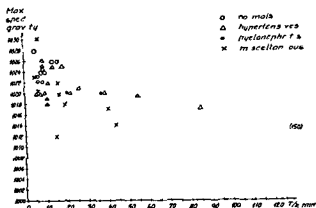


Fig 4 Relationship between half life for the descending phase of the nephrogram (T/2 computed) and the concentration power of the kidney The figure includes only patients with no disparity and T/2 calculated represents the mean value for the two sides

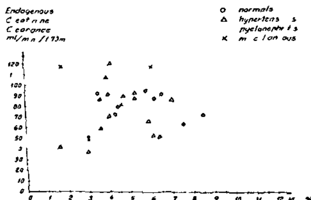


Fig 5 Relationship between maximum activity in the nephrogram expressed as a percentage of the injected dose and endogenous 24 hour creatinine clearance The figure includes only patients with no disparity and the max value represents the mean value for the two sides

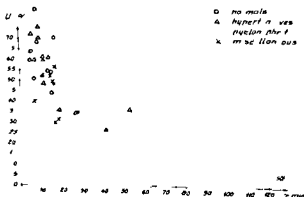


Fig 6 Relationship between half life for the descending phase of the nephrogram (T/2 calculated) and the urinary excretion of radioactivity in per cent of the dose 40 min after the injection (U) The figure includes only patients with no disparity and T/2 computed represents the mean value for the two sides

as well as in cases without arteriographic evidence of such stenosis These phenomena will be discussed in more detail in a subsequent paper 5)

In the presence of unilateral papillary necrosis there was a definite and relevant disparity in 4 of 6 patients This is illustrated in fig 2 There is nothing surprising

Table V The cases showing a disparity between the right and left isotope nephrography

Diagnosis	No of pts	Disparity
Hypertension with renal artery stenosis	5	5 (100%)
Essential hypertension	21	6 (29%)
Pyelonephritis with unilateral papillary necrosis	6	4 (67%)
Pyelonephritis without unilateral papillary necrosis	9	3 (33%)
History of nephrectomy	3	3 (100%)
Unilateral hydronephrosis	1	1
Renal tumour	2	2
Pelvic calculus	1	1
Acute glomerulonephritis	3	1
Other diseases	7	0
Normal	10	1 (10%)
Total	68	27

about an asymmetric nephrogram in some cases of chronic pyelonephritis without papillary necrosis

In the remaining patients showing a disparity the cause is evident Previous nephrectomy, unilateral hydronephrosis, renal tumour, or pelvic stone Following nephrectomy there is a certain activity at the site of the blood flow through the soft tissues on the operated side, but no uptake is seen over the remaining kidney In one normal subject (case 67, table I) and in one patient with glomerulonephritis (case 33, table IV) there was an unexplained disparity

In hydronephrosis (fig 7) the nephrogram is altered in a way which differs fundamentally from all the other renal diseases mentioned above The typical finding is a marked prolongation of t and T/2, i e a very slowly rising and falling curve, whereas the max value is normal This appearance is observed in the presence of ureteric obstruction with preserved renal function

Discussion

There are various fundamental problems to be considered in connection with isotope nephrography

A primary question is the selection of the parameters Those used in the present study have the advantage of being simple and easy to fix The half-life (T/2) has proved to be a sensitive indicator of renal function and urine flow, and in our studies it has been the one which has afforded the apparently most useful information The maximum value decreases in any type of renal functional impairment, but it carries quite marked inaccuracy, due primarily to the importance of centering over the kidney We observed that the slightest change in the patient's position during the study appreciably affected the recorded activity Accurate centering over the kidney is decisive as far as the maximum value is concerned, whereas it does not affect the shape of the curve, i e the half life Indeed, this has been stressed by several authors (13, 17, 19, 21) Stewart and Haynie (18) have taken particular interest in this aspect They found a disparity in the maximum value on the right and left exceeding 20 % in half their patients with essential hypertension, whereas half the patients with renal artery stenosis had a disparity in the maximum values on the right and left of less than 20 % Consequently, these authors disregarded the maximum value entirely in assessing the curves, basing their conclusions only on t and T/2 The same authors tried using other parameters, such as the height and the slope of the initial phase and the activity at the end of 15 min , but they found these parameters of no major value As regards the time from injection to maximum activity (t) the absolute value did not give us valuable information, while a disparity between the

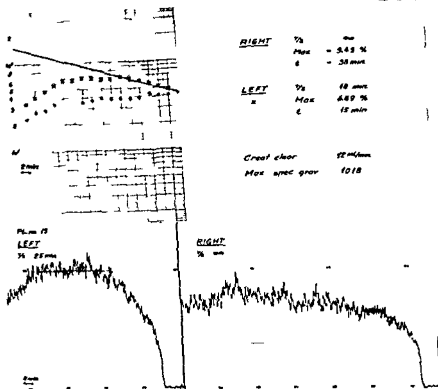


Fig 7 Nephrogram in a case of right sided hydronephrosis (case 13 table IV) For abbreviations, cf table I

two sides was more important In 14 patients there was a definite disparity in t, and in other diagnostic procedures 9 of these patients were found to have unilateral disease either renal artery stenosis papillary necrosis, hydronephrosis hypoplasia renal tumour or they had a history of nephrectomy

It is a different problem altogether whether the various phases of the nephrogram may be related to the various partial functions of the kidney i e blood flow filtration rate tubular function, and urine flow

As already mentioned the first phase was originally thought to represent the blood flow while the secondary rise was believed to represent tubular function and the descending part of the curve the excretion in the pelvis and the urine flow However, thorough investigations chiefly by Wax and McDonald (21) showed that this division cannot be maintained The first so-called 'vascular' phase, is due predominantly to the functional capacity of the kidney, in the form of glomerular filtration and tubular secretion, and only to a minor extent to its vascular capacity Klapproth et al (7), who have also analysed this problem believe that each phase of the nephrogram consists of at least 3 components These views are in keeping with our present studies which show that the descending part of the ne

phrogram i e the half life, is in negative correlation to glomerular filtration as well as to tubular function

Generally, an abnormal nephrogram does not justify any aetiological diagnosis, as has been emphasized by Doig et al (3) An exception is, as already mentioned, postrenal obstruction with preserved renal function, in which there will be a slowly rising and slowly falling curve of a normal height An attempt has been made to utilize this in diagnosing acute abdominal conditions, as this appearance will be found in the presence of a ureteric stone The nephrogram also appears to be able to yield information in acute anuria, as bilateral ureteric obstruction is accompanied by this very type of curve while diffuse, ischaemic nephropathy ("shock kidney") is associated with a flat curve with a reduced maximum value (8)

Summary and conclusion

Isotope nephrography, using ^{131}I sodium ortho iodo hippuric acid was done on 10 normal subjects and 58 patients suffering from various renal diseases

The normal values of the parameters employed and the criteria of disparity between the two sides are set up

Isotope nephrography affords information about the function of each kidney separately The maximum activity obtained and the speed at which the activity decreases bear a definite relationship to glomerular filtration rate as well as tubular function Thus the various phases of the nephrogram cannot be consistently correlated to the various renal functions

In 8 patients with nephropathy and phenacetin abuse nephrography was carried out before and after administration of phenacetin 3 g daily for 10 days Only one of the patients showed a definite exacerbation of the parameters during the test

A disparity in the nephrograms of the two sides was found in 27 of the 68 patients In 16 of these patients the explanation was easy to detect, being renal artery stenosis, unilateral papillary necrosis, a history of nephrectomy, unilateral hydronephrosis, renal tumour, or pelvic calculi In the remaining 11 patients the diagnoses were essential hypertension (6), chronic pyelonephritis (3), acute glomerulonephritis (1), and no abnormality (1)

Thus isotope nephrography usually gives no aetiological information the different renal diseases giving rise to the same nephrographic changes viz a low and slowly falling curve However, postrenal obstruction appears to give a more specific appearance, consisting in a slow rise and a slow fall, with preserved maximum value

It is an advantage of this procedure that it is technically easy and causes the patient no discomfort Our results show that it may be carried through with a single unit although of course a double unit is preferable

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phrogram, i. e. the half life, is in negative correlation to glomerular filtration as well as to tubular function.

Generally, an abnormal nephrogram does not justify any aetiological diagnosis, as has been emphasized by Doig et al. (3). An exception is, as already mentioned, postrenal obstruction with preserved renal function, in which there will be a slowly rising and slowly falling curve of a normal height. An attempt has been made to utilize this in diagnosing acute abdominal conditions, as this appearance will be found in the presence of a ureteric stone. The nephrogram also appears to be able to yield information in acute anuria, as bilateral ureteric obstruction is accompanied by this very type of curve, while diffuse, ischaemic nephropathy ("shock kidney") is associated with a flat curve with a reduced maximum value (8).

Summary and conclusion

Isotope nephrography, using ^{131}I-sodium-ortho-iodo-hippuric acid was done on 10 normal subjects and 58 patients suffering from various renal diseases.

The normal values of the parameters employed and the criteria of disparity between the two sides are set up.

Isotope nephrography affords information about the function of each kidney separately. The maximum activity obtained and the speed at which the activity decreases bear a definite relationship to glomerular filtration rate as well as tubular function. Thus, the various phases of the nephrogram cannot be consistently correlated to the various renal functions.

In 8 patients with nephropathy and phenacetin abuse, nephrography was carried out before and after administration of phenacetin, 3 g daily for 10 days. Only one of the patients showed a definite exacerbation of the parameters during the test.

A disparity in the nephrograms of the two sides was found in 27 of the 68 patients. In 16 of these patients the explanation was easy to detect, being renal artery stenosis, unilateral papillary necrosis, a history of nephrectomy, unilateral hydronephrosis, renal tumour, or pelvic calculi. In the remaining 11 patients the diagnoses were essential hypertension (6), chronic pyelonephritis (3), acute glomerulonephritis (1), and no abnormality (1).

Thus isotope nephrography usually gives no aetiological information, the different renal diseases giving rise to the same nephrographic changes, viz. a low and slowly falling curve. However, postrenal obstruction appears to give a more specific appearance, consisting in a slow rise and a slow fall, with preserved maximum value.

It is an advantage of this procedure that it is technically easy and causes the patient no discomfort. Our results show that it may be carried through with a single unit, although of course a double unit is preferable.

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Isotope Nephrography with ¹³¹I "Hippuran"

II Experience in Arterial Hypertension with a Particular View to Renal Artery Stenosis

By

TH FRIIS and A R KROGSGAARD

The recognition of unilateral renal disease in arterial hypertension is of theoretical and therapeutic importance In renal artery stenosis the results of surgery are often superior to those in other unilateral kidney diseases (3 4 10, 16) As emphasized in the literature, stenosis of the renal artery is not uncommon Its incidence has been reported as 20 % among selected inpatients suffering from hypertension (1, 9 17, 22) Hoobler (8) and Freis (6) however mention an incidence of 2 5 % and a maximum of 5 % in servere hypertension The most common cause of stenosis is said to be atheromatous plaques (3) but thromboses emboli fibromuscular hyperplasia and congenital anomalies may also be responsible

The history and ordinary clinical investigation often do not give sufficient diagnostic information It has been pointed out that sudden onset of hypertension ought to give rise to suspicion and so should a malignant course early age lowback pain, history of injury to the lumbar region, signs of hyperaldosteronism, absence of hereditary predisposition to hypertension As stressed by Poutasse (17), however, none of these criteria are decisive and they may also be absent Lastly, it has been stated that in 50 % of the cases auscultation may reveal a blowing sound over the affected kidney (3, 17)

Among diagnostic aids we have primarily pyelography In the presence of renal artery stenosis it will show a diminution of the kidney, narrowing of the parenchyma, and a delayed or reduced excretion of the contrast, presumably because of a reduced urine flow (3) According to Poutasse (17) the pyelograms are instructive in 70—80 % of the cases Hodson (7) has recommended supplementing the investigation by tomography in order to obtain better data about the relative size of the structures However, at times the pyelograms are normal in cases of arterial stenosis, so that other diagnostic methods

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Table I Renal function and nephrography in 15 hypertensive patients showing no disparity between the two sides

Case no	Sex	Age	B P	Eye ground	Serum creatinine (<1.3 mg/100 ml)	Creatinine clearance[2] (>67 ml/min)	Max concentration (>1,022)	T/2 measured (<20 min)		T/2 computed (<20 min)		Max (>20%)		t (<7 min)		U (>45%)	
								Left	Right	Left	Right	Left	Right	Left	Right		
40	♂	25	165/105	I	1.0	108	1,025	6	7	13	14	4.1	3.8	3	3	64	60
60	♀	62	190/110	I	1.0	91	1,022	10	12	11	11	4.0	4.3	3	5	63	60
76	♀	40	230/110	II	1.1	90	1,025	14	12	10	12	5.2	4.1	7	5	60	61
81	♂	49	210/125	II	1.3	93	1,026	6	9	11	10	5.2	5.8	5	5	61	—
77	♂	55	250/120	II	1.2	78	1,020	7	10	9	8	3.8	5.5	7	5	68	77
30	♂	18	160/110	0	1.0	122	1,020	8	—	11	11	3.1	5.3	5	7	43	53
78	♂	33	160/100	0	1.2	78	1,018	8	16	9	16	3.7	6.1	5	5	75	86
42	♂	38	180/110	I	0.9	86	1,020	8	8	7	6	5.9	8.2	5	7	51	70
73	♂	60	260/130	II	1.2	70	1,019	12	12	12	12	4.3	3.6	7	5	46	58
46	♀	64	240/100	0	1.1	53	1,025	16	10	16	20	7.2	5.4	7	7	28	43
54	♀	68	220/105	I	1.3	60	1,021	20	24	24	28	4.2	3.1	7	13	35	—
48	♀	56	250/140	III	1.1	66	1,020	30	20	22	24	5.0	6.8	7	9	—	—
72	♀	47	250/140	II	1.1	77	1,020	36	50	40	40	3.7	3.6	7	9	25	31
5	♀	64	210/110	III	1.5	52	1,017	60	46	84	84	6.4	6.4	20	20	—	—
82	♂	58	190/120	II	2.0	46	1,020	60	60	64	44	1.7	1.4	3	5	34	38

T/2 measured = Time from maximum value to half this value has been reached on the descending phase, measured on the curve traced by the recorder
T/2 computed = Half life in a semilogarithmic system for the descending phase
Max = Maximum value over the kidney in % of the dose
t = Time from injection until the maximum value over the kidney has been attained
U = Urinary output of radioactivity in % of the dose 40 min after injection

[1] Illustrated on fig 1
[2] Calculated in relation to 1.73 m² body surface

have been adopted (2, 20, 24), among others the "split function test" introduced by Howard et al (11, 12), and modified by Stamey (21), Rapoport (18) and others In the presence of unilateral stenosis there will be a lower concentration of sodium in the urine and a lower urinary output from the affected side while the creatinine concentration will be increased Incidentally, the functional appearances in renal artery stenosis have recently been described in more detail by Kjellbo et al (13)

In recent years, as also mentioned in our previous paper (14), isotope nephrography using ^{131}I-labelled sodium ortho-iodohippuric acid (Hippuran) has come into use, and a number of publications on this subject have seen the light of day (5, 20, and others) Stenosis of the renal artery as a rule gives rise to a disparity in the renograms on the two sides Emphasis has been placed partly on a *different height* of the two curves and partly on a difference in the rate of the rise and fall 15 22 23) However, the method does not by

Table II Renal function and nephrography in 6 hypertensive patients showing disparity between the two sides but no arterial stenosis

Case no	Sex	Age	B P	Eye ground	Serum creatinine (<1 3 mg/100 ml)	Creatinine clearance[2] (>67 ml/min)	Max concentration (>1 022)	T/2 measured (<20 min) Left	T/2 measured (<20 min) Right	T/2 computed (<20 min) Left	T/2 computed (<20 min) Right	Max (>2 0 %) Left	Max (>2 0 %) Right	t (<7 min) Left	t (<7 min) Right	U (>45 %)		
61	♀	47	190/130	II	1.3	70	1 020	20	13	16	11	*3 6*	*11.9*	7	5	48	50	—
64	♀	52	170/100	0	1 1	72	1 020	14	12	8	10	*8.7*	*4 2*	7	5	52	51	—
[1]39	♀	40	190/140	II	0 9	66	1 019	8	12	24	20	*7 4*	*3 1*	*3*	*9*	32	28	—
4	♂	60	210/110	III	1 5	60	1 017	14	24	*14*	*28*	3 3	2 1	11	7	—	—	—
75	♀	36	240/140	II	1 2	66	1 025	*16*	*40*	*14*	*54*	9 5	6 3	*7*	*15*	71	57	Hypoplasia of right kidney
80	♂	42	210/150	II	1.2	100	1 024	∞	*14*	*70*	*8*	*1 0*	*9 8*	*3*	*9*	62	69	Calc. tub of left kidney

For explanation of abbreviations cf table I
The italicized figures indicate disparity between the two sides

[1] Illustrated in fig 2
[2] Calculated in relation to 1 73 m² body surface

any means guarantee a correct diagnosis There may be a disparity between the two sides without arterial stenosis due to deficient centering of the crystal or other causes of differences in renal function, and there may also be stenosis despite a normal nephrogram (5) Stewart et al (22) for instance found false positive nephrograms i e disparity in 11 out of 44 hypertensive patients without renal artery stenosis and false negatives in 5 out of 20 patients with proven stenosis These 5 patients however had either bilateral or segmental stenosis Nevertheless the procedure is said to be on the whole more contributive than pyelography (22) Doig et al (5) reported that only 3 out of 7 patients with stenosis showed abnormal pyelograms while 6 had abnormal nephrograms

Material and methods

On a fairly small series of hypertensive patients we tested the technique described in our previous paper (14) This series comprised a total of 26 patients with fixed hypertension It is selected including mainly patients who were suspected of arterial stenosis but it is not by any means unusual for a medical department

The patients may naturally be divided into 3 groups 1) patients without a disparity in the nephrogram a total of 15 2) patients showing disparity in the nephrograms but normal aortography (the Radiological Department of the University Hospital (Rigshospitalet)) by the Seldinger (18) method a total of 6 and 3) patients showing disparity in the nephrogram and aortographic evidence of arterial stenosis a total of 5

The nephrogram was taken to show a disparity only if one of the three following parameters (14) was doubled or halved

T/2 computed = half line for the descending phase of the activity over the renal region plotted in a semilogarithmic system

Table III Renal function and nephrography in 5 hypertensive patients with arterial stenosis

Case no	Sex	Age	B P	Eye ground	Serum creatinine (<1 3 mg/100 ml)	Creatinine clearance[2] (>67 ml/min)	Max concentration (>1 022)	T/2 measured (<20 min) Left	T/2 measured (<20 min) Right	T/2 computed (<20 min) Left	T/2 computed (<20 min) Right	Max (>2 0 %) Left	Max (>2 0 %) Right	t (<7 min) Left	t (<7 min) Right	U (>45 %)	U (>45 %)	
[1]10a	♀	56	250/150	II	1 3	61	1 017	∞	*16*	*140*	*30*	2 5	3 1	7	5	—	—	Constriction of left ren art Howard test (+)
10b			230/130	II	2 2	24	1 011	∞	*32*	*168*	*36*	3 7	4 4	7	7	—	—	After oper
[1]6a	♂	48	250/150	II	1 2	88	*1,020*	*11*	*6*	*20*	*4*	3 9	6 1	5	5	—	—	Constriction of left ren art Howard test +
6b			225/150	III	1 4	70	1,018	—	12	*102*	*15*	2 7	4 2	*7*	*3*	—	—	After oper
[1]6c			205/135	II	1 3	86	1 021	*44*	*6*	*46*	*7*	*2 4*	*7 8*	*11*	*5*	54	41	After oper
[1]3	♂	59	210/130	III	2 1	49	1 028	*17*	*66*	*29*	*53*	*2 8*	*1 1*	5	5	—	—	Constriction of right ren art
9	♂	56	200/120	II	1 3	44	1,025	*44*	*22*	42	34	1 9	1 2	7	9	—	—	Constriction of left ren art Howard test —
41	♂	65	*220/110*	*III*	2 5	38	*1 015*	36	—	*56*	*170*	3 9	*2 1*	*7*	*15*	24	*22*	Constriction of right ren art

For explanation of abbreviations cf table I

The italicized figures indicate disparity between the two sides

[1] Illustrated on figs 3—6

[2] Calculated in relation to 1 73 m² body surface

T/2 measured = the time elapsing until the activity over the kidney has decreased by one half read direct on the curve traced by the recorder

Max = maximum value of activity over the renal region expressed as a precentage of the dose

t = time from injection until the maximum activity over the kidney has been attained

Table I lists the data for the 15 hypertensive patients who showed no disparity in the nephrograms The first 4 had normal renal function assessed by the usual tests, including pyelography The nephrograms were normal in all cases showing normal parameters and activity in the urine The next 5 had a slightly recuded

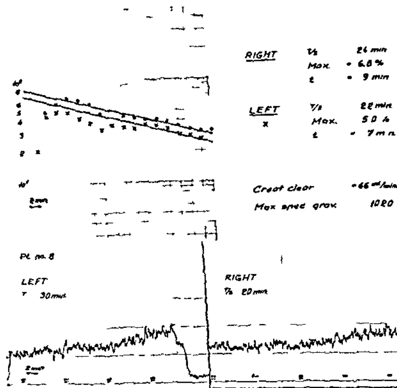


Fig 1 Nephrography of case 8 (table I) Hypertension no disparity between the two sides The upper curves on the left represent the value plotted in a semilogarithmic system The 2 lower curves were traced by the recorder and should be read from right to left

concentration power but normal nephrograms The excretion of Hippuran as well as the creatinine clearance were normal The last 6 patients had reduced creatinine clearance and concentration power (except one with a normal concentration power and one with a normal clearance) and at the same time nephrography showed abnormal values for both kidneys apart from case 46 who merely had a low urinary output of radioactivity

Table II sets out the 6 patients showing disparity in the nephrogram but no aortographic signs of arterial stenosis In case 75 aortography revealed signs of some hypoplasia of the right kidney Case 80 had tuberculosis of the left kidney with calcifications in the renal pelvis and parenchyma The disparity in the nephrograms was in conformity with this finding but showed a divergence in a direction different from the other parameters In the other 4 patients the investigations, including pyelography and arteriography, failed to disclose any cause of the disparity

Table III lastly, shows the findings in the 5 patients in whom arterial stenosis was diagnosed It will be seen that cases 10 and 6 were investigated twice and three times respectively All 5 patients showed a marked disparity in respect to the descending phase of the curves while only 2 showed a difference in maximum

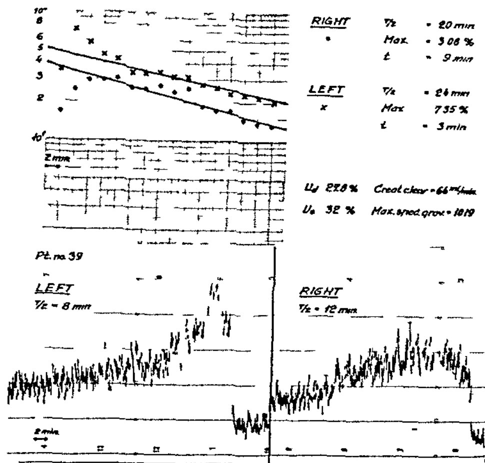


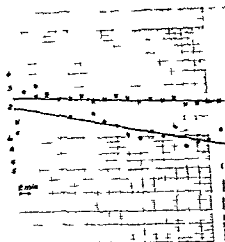
Fig 2 Nephrography of case 39 (table II) Hypertension disparity but no stenosis For explanation cf fig 1

height and 2 a difference in the ascending phase

Some items of these case histories seem worth emphasizing in some detail

Case reports

Case 10 was a 56 year old woman who developed *dizziness* and headache about the New Year of 1962 In January 1962 she was admitted to Medical Dept E where she was found to have fixed hypertension of about 250/150 eyeground changes corresponding to hypertonic fundus II a creatinine clearance of 61 ml/min a maximum concentration power in the kidney up to a specific gravity of 1 017 a normal phentolamine test and catechol amine excretion in the urine and normal pyelography Tomography however gave rise to a suspicion *of hypoplasia of the left kid*ney The Howard test did not yield consistent results since the sodium as well as creatinine concentration were reduced on the left Nephrography *revealed a prolonged descending* phase on the left (fig 3 and table III case 10 a) and aortography disclosed stenosis of the left renal artery 6 mm from the aorta The stenosis was 4 mm in length and 1 mm in diameter as compared with a calibre of 7 mm at the aorta There was a post stenotic dilatation and poor filling of the left kidney On the right two normal renal arteries were visualized Operation was performed in Surgical Department D of the University Hospital and revealed thrombosis in the *left renal artery* The thrombosis was removed and the narrowed segment of the artery excised whereupon a patch from the great saphenous vein was inserted Pressure measurements in the artery were not performed Biopsy from the left kidney showed normal appearances After the operation the serum creatinine rose to 2 0 mg/100 ml Pyelography now showed lacking



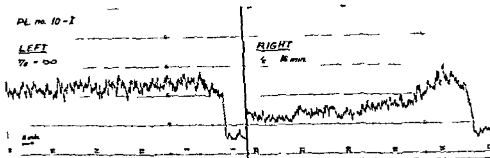


Fig 3 Nephrography of case 10 a (table III) Before operation Hypertension disparity and stenosis on the left For explanation cf fig 1

excretion on the left and repeated aortography total occlusion of the left renal artery as well as occlusion of the distal part of the two renal arteries on the right There was poor filling of the distal part of the right kidney and hardly any filling at all on the left

The patient was returned to Department E in Aug 1962 Her hypertension was found to be unchanged 230/130 and the renal function had considerably deteriorated (table III case 10 b Repeated nephrography accordingly showed a somewhat longer descending phase and still a marked disparity between the two sides The patient has been attending as an out patient ever since The hypertension has proved relatively refractory All the time she has shown a tendency to hypotassaemia

Case summary A 56-year old woman with hypertension and normal serum creatinine as well as pyelography Tomography gave rise to a suspicion of hypoplasia of the left kidney Nephrography revealed impaired function on the left and aortography disclosed stenosis of the left renal artery Endarterectomy was carried out but after the operation occlusion occurred anew in the left renal artery as well as in a branch of the right renal artery Renal function deteriorated and the hypertension remains unchanged

Case 6 was a man aged 48 who developed headache in 1958 In 1960 he was admitted to Frederiksberg Hospital Medical Dept E where a fixed hypertension of about 250/150 was found The eyeground was normal and so was the creatinine clearance but the maxi

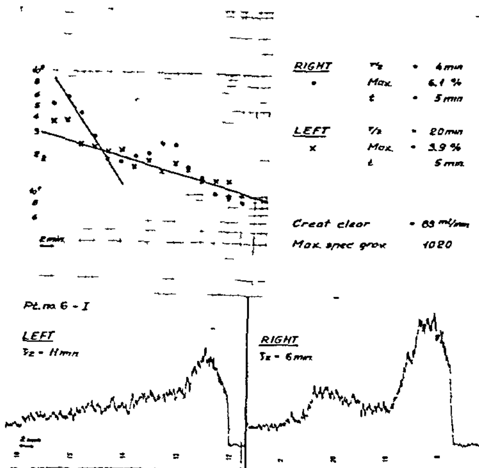


Fig. 4. Nephrography of case 6 a (table III). Before operation. Hypertension disparity, stenosis on the left. For explanation cf. fig. 1.

mum concentration power was only 1.017. There was no hypopotassaemia. He was treated by medication and re-admitted in the summer of 1961 with transient right sided hemiparesis. His B.P. was unchanged. He had developed an eyeground change corresponding to hypertonic fundus II, serum creatinine 1.2 mg/100 ml, creatinine clearance 88 ml/min and a maximum concentration power of 1020 (table III, case 6 a). Pyelography showed a somewhat delayed excretion on the left, and tomography suggested that the left kidney was smaller than the right. Nephrography (fig. 4) revealed normal paremeters but disparity in the maximum height and descending phase, the function of the left kidney appearing to be inferior to that of the right. The Howard test indicated ischaemia of the left kidney. Seldinger aortography confirmed the diagnosis of constriction of the left renal artery which was only 3 mm at its departure from the aorta. The parenchymatous filling was found to be poorer on the left than on the right.

Now endarterectomy of the left renal artery was carried out at the University Hospital, Surgical Dept. D. There was a firm thrombus, 2 cm in length, and plastic repair of the renal artery was performed. Since, however, the systolic pressure in the renal artery was only 50 mm Hg, the artery was incised again, and a patch from the great saphenous vein was inserted. Thereafter, the pressure in the renal artery was 95/85 and in the aorta 175/150. However, this can hardly be considered satisfactory (3). The B.P. was unchanged on discharge.

Two weeks later (in August 1962) the patient was re-admitted to Dept. E in hypertensive crisis with a B.P. of 300/200. He was treated with phenobarbitone and ganglion blocking agents and the B.P. then fell to a normal value

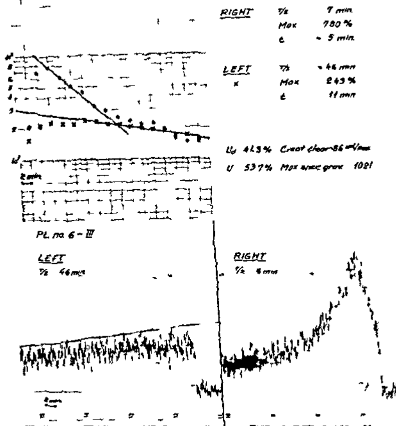


Fig 5 Nephrography of case 6 c (table III) After operation Hypertension disparity stenosis on the left For explanation cf fig 1

Nephrography was performed again (table III case 6 b) It showed a marked disparity be tween the two sides in the ascending as well as in the descending phase However the right kidney still appeared to have normal function The creatinine clearance was 70 ml/min and the maximum concentration power 1 018 Since the patient was still suffering from head ache and dizziness and since the B P was in reasing despite treatment nephrectomy was contemplated Repeated nephrography (fig 5 and table III case 6 c) showed changes as be fore viz normal function on the right but abnor mal on the left The patient was therefore transferred to Dept A where left-sided ne phrectomy was performed in January 1963 There were no signs of thrombosis in the left renal artery

The removed kidney was grossly normal 4 × 5 × 9 cm with an easily detached cap sule Microscopic study revealed normal glo- meruli The proximal convoluted tubules however were dilated Henle s loop slightly atrophic showing increased quantities of con nective tissue The distal convoluted tubules were also fairly ectatic containing a number of white cells and macrophages in some of which hyaline deposits were present

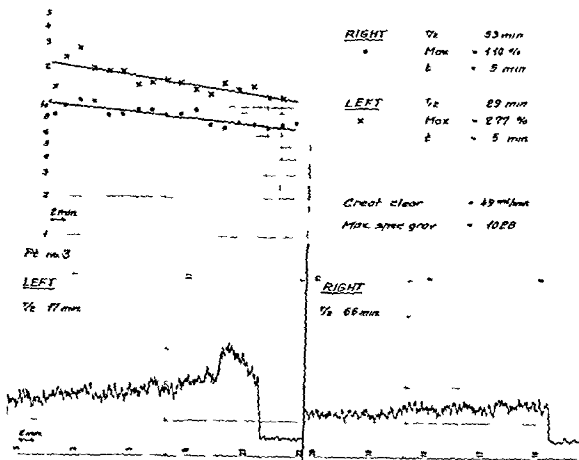


Fig 6 Nephrography of case 3 (table III) Hypertension, disparity, stenosis on the right For explanation of fig 1

The vessels appeared normal Histological diagnosis Mild acute and chronic inflammatory changes

After the nephrectomy the B P fell to about 170/100 On the following days there were a few paroxysms of hypertensive episodes during which the B P rose to about the preoperative values (250/150), but they subsided

The patient is attending the out patient Clinic, and his B P has kept around 150/100 without treatment He is feeling well and capable of working The serum creatinine is normal

Case summary A 48-year-old man with hypertension and normal serum creatinine in whom pyelography revealed delayed excretion on the left Nephrography showed poorer function of the left kidney than the right, and aortography disclosed stenosis of the left renal artery Left-sided endarterectomy was performed without any effect upon the B P , and 2 repeated nephrographies still showed impaired function of the left kidney After left-sided nephrectomy the B P fell to normal values

Case 3 was a 59 year old man who was admitted with headache to the Frederiksberg Hospital Medical Dept B in April 1962 His B P was found to be elevated about 210 130 and he showed hypertonic fundus III serum creatinine 2 1 mg/100 ml creatinine clearance 49 ml/min and a maximum concentration power of 1028 (table III case 3) Serum electrolytes were normal without any signs o hypopotassaemia

Pyelography revealed reduced excretion on both sides The right kidney was strikingly small and this was confirmed by tomography Nephrography (fig 6) showed abnormal appearances on both sides (prolonged T/2 low maximum), but with a marked disparity, T/2 and maximum indicating poorer function of the right than the left kidney Aortography showed non filling of the right renal artery and no filling of the right kidney unlike the left

The Howard test failed as no urine was flowing from the right kidney In connection with the Howard test, incidentally the patient had anuria for 24 hours and the serum creatinine rose to 6 7 mg/100 ml

Right sided nephrectomy was contemplated but was given up as there were no signs of infection in the right kidney and as the serum creatinine was elevated indicating nephrosclerosis in the left kidney — in accordance with the nephrographic findings

The hypertension was treated by drugs with some effect However, the patient was re admitted with visual impairment in the right eye and thrombosis was found in the left central artery He is still on medication and the B P has fallen to about 180/100

Case summary A 59 year old man with hypertension and elevated serum creatinine in whom pyelography suggested hypoplasia of the right kidney Nephrography showed poorer function of the right kidney than the left and aortography disclosed stenosis of the right renal artery

Case 9 was a 56-year-old man repeatedly admitted to Bispebjerg Hospital Dept C for the first time in 1962 with left sided hemiparesis The B P was found to be 200/120 and there was hypertonic fundus II serum creatinine 1 3 mg/100 ml creatinine clearance 44 ml min and maximum concentration power 1 025 The Howard test did not show any disparity between the two sides Pyelography revealed normal excretion seriography slightly delayed excretion on the right where a ureterocele was demonstrated

Nephrography disclosed abnormal appearances on both sides There was a low maximum value and a prolonged descending phase In particular the T/2 was prolonged on the left side i e the side opposite to the ureterocele Aortography showed good filling of both renal arteries and their branches There was however perhaps a constriction at the departure of the left renal artery Repeated investigations revealed that the left renal artery was narrowed at its departure from the aorta being only 4 mm in diameter while a couple of cm from the departure it was 11 mm Owing to the cerebral complications and a presumed bilateral renal disease operation was not performed

Case summary A 56 year old man with hypertension and normal serum creatinine as well as pyelographic appearances, in whom nephrography showed poorer function of the left kidney than the right Aortography disclosed stenosis of the left renal artery

Case 41 was a man aged 65 who was admitted to Medical Dept E with fixed hypertension of about 220/140 with hypertonic fundus III and impaired renal function Serum creatinine 2 5 mg/100 ml creatinine clearance 38 ml/min and maximum concentration power 1 015 Serum electrolytes were normal and so were the phentolamine test and noradrenaline output The hypertension had been present for years but its exact duration was unknown Pyelography showed poor excretion on both sides Nephrography revealed highly abnormal appearances on both sides (table III case 41) but with distinct disparity between the two sides the ascending as well as the descending phase indicating that function was poorer in the right kidney than in the left Aortography disclosed stenosis of the right renal artery at its departure from the aorta and post stenotic dilatation Since the left kidney was affected too operation was not performed especially as signs of heart failure were present

Case summary A 65 year old man with hypertension and elevated serum creatinine Pyelography showed poor excretion on both sides Nephrography revealed poorer function of the right kidney than the left, and aortography disclosed stenosis of the right renal artery

Discussion

As already mentioned the series is small, but it does include hypertensive patients without any disparity in the nephrograms (15), hypertensive patients showing disparity, but no aortographic signs of arterial stenosis (6), and patients showing disparity in the nephrograms as well as aortographic evidence of arterial stenosis (5) On the other hand, we are unable to state whether arterial stenosis was present among the patients without any disparity in the nephrograms, as the majority of these patients did not have aortography According to the literature, however, there may be cases showing false negative nephrograms (5, 22), so that the method is hardly applicable as the sole screening test for renal artery stenosis Yet, it is indubitably a good supplement to the current investigations for assessing differences in the function of the 2 kidneys, it is technically easy, and it causes the patients no discomfort Moreover, it is valuable for assessing the function of each kidney separately For instance, it appears to be able to show whether one kidney is functioning normally, which is of extremely great importance if the other kidney is to be removed It is also applicable for following the operative result after endarterectomy as pointed out by Stewart et al (22)

A factor of great importance is whether the nephrogram is of a specific appearance in the presence of renal artery stenosis According to Nordyke et al (15) a prolongation of the ascending phase is typical of renal artery stenosis while a less marked prolongation of the descending phase is of no significance Wax et al (23) on the other hand, consider the descending phase more important, as they have found a slower rate of fall in patients with stenosis This finding they have related to reduced urinary flow We found a difference in the ascending phase in only 2 cases, while all the patients with stenosis showed a difference in the descending phase

Nephrography should presumably be used concurrently with pyelography in cases of severe hypertension If either of these procedures shows a disparity between the two sides, aortography is indicated Out of our 5 patients with arterial stenosis, pyelography had given rise to a suspicion in 2 (cases 3 and 6), and in yet another (case 10) tomography was suggestive In the other 2 patients (cases 9 and 41) the named radiographic procedures did not contribute to the diagnosis

As far as the clinical symptoms in the stenotic cases are concerned, the hypertension had been of a sudden onset in at least 2 (cases 6 and 10), it was fixed and severe in all the patients and moreover refractory to medication in at least the 3 patients (cases 6, 10, and 41) who have been followed for a long time

Summary

Isotope nephrography was performed on 26 patients with fixed hypertension In 15 the nephrograms showed no disparity between the two sides, in 6 there was disparity but no aortographic signs of arterial stenosis, while 5 had disparity in the nephrograms as well as aortographic evidence of arterial stenosis Two were treated by endarterectomy with no effect One had nephrectomy which normalized the blood pressure Pyelography and nephrotomography had suggested arterial stenosis in 3 of the patients who had arterial stenosis

In our experience isotope nephrography is technically easy and causes the patients no discomfort It is well suited for assess-

ing the function of each kidney separately This procedure will presumably disclose the majority of cases of unilateral stenosis in the major renal arteries, but according to the literature it may occasionally fail Therefore, it is probably not suitable as the sole screening test for disclosing stenosis in the renal artery

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Chlornaphazin (Erysan©) May Induce Cancer of the Urinary Bladder

By

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Chlornaphazin (MTN) or Erysan (chloronaphtina, R48 CB1048) is a derivative of 2 naphthylamine (cf fig 2) in which each of the 2 hydrogen atoms belonging to the N atom has been replaced by chloroethyl groups (N,N bis(2 chloroethyl) 2 naphthylamine) The drug was developed by Ross in 1949, and Haddow demonstrated its pronounced cytostatic effect upon experimental tumours Chlornaphazin has no immediate side effects it has no particular local irritating effect it is freely soluble in water and easily absorbed from the intestinal tract It seemed reasonable therefore to test it *in the* treatment of malignant systemic diseases After Matthews (9) in 1950 had reported its clinical effect without any *major side-*effects it was used a good deal, both in Italy and in Denmark Iversen and Meulengracht (8) have reported its use *in inter alia* polycythaemia vera, Videbæk and Kaae (14) especially in Hodgkin s disease and Piper (10) in polycythaemia vera In the present author s experience from the subsequent years chlornaphazin was a satisfactory agent in controlling the fever, itching, weight loss, and sweating associated with *the more advanced stages* of Hodgkin s disease, *if administered* in fairly small doses (200—400 *mg daily*) but for prolonged periods i e *months or perhaps* years

But now within a few months, the author has observed the *development of* bladder carcinoma in 3 *patients, two of* whom are young, *who had been treated* with chlornaphazin *for long periods* Since *investigations* into the biochemistry of bladder carcinoma (in particular by Boyland, and mainly recent) indicate that in *the* urine chlornaphazin is most likely *metabolized* to a strong carcinogen this *serious* complication is not surprising — *and* may almost be called a logical consequence However, this evidently great risk of cancer has been unheeded Since *the* growths observed by the author *developed after a relatively* short period of *treatment, the three* cases will be briefly *reported below,* especially in relation to the chlornaphazin therapy Lastly, the probable explanation of the carcinogenic *effect* of the drug will be discussed

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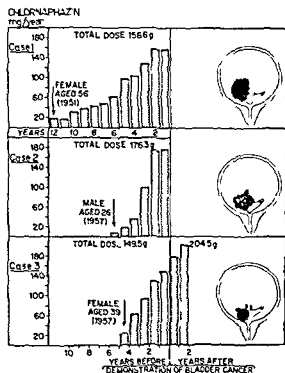


Fig 1 Cumulative dosage of chlornaphazin in 1 case of polycythaemia vera (case 1) and 2 cases of Hodgkin's disease (cases 2 and 3) in relation to the time of detection of bladder carcinoma

Case reports

Case 1 A housewife, born in 1895 One delivery in 1926, menopause in 1929 Mild arterial hypertension was diagnosed about 1948, and polycythaemia vera in 1951 (Medical Department, Central Hospital Hillerod) on the basis of her appearance, a haemoglobin level of 161 %, R B C 7 82 mill E S R 0 mm serum uric acid 8 6 mg/100 ml, W B C 8,280 with 14 % netrophil rod shapes and 72 % neutrophil segm I v pyelography normal Spleen not enlarged W R negative

Treated with chlornaphazin as shown in fig 1, and received a total of 156 6 g in 10 years Never treated with X-rays or P^{32} In 1962 the patient started complaining of retrosymphyseal pain the urine became cloudy and foul smelling, and micturition was frequent and painful Referred to the Radium Centre, Copenhagen, where cystoscopy revealed a reddish tumour on a wide base lined with fibrin and shaped like a bunch of grapes The tumour measured about 2 × 3 cm it occluded the orifice of the right ureter and showed dissemination towards the left ureteral orifice The mucous membrane was slightly reddened in the trigonum, but elsewhere of normal appearance Biopsy Solid carcinoma

Owing to a firm, immovable infiltration towards the right pelvic wall, the tumour was considered inoperable, so in April 1963 the patient was treated with telecobalt (Mobaltron), distance 80 cm 5550 r/33 days, so far with a good result Serum creatinine 1 4 mg/100 ml, E S R 6—7 mm, Hb 116 %

Case summary A 68-year old woman who had been suffering from polycythaemia vera for 12 years For 10 years she had been treated periodically with chlornaphazin, a total dose of 156 6 g and thereafter developed a cancer of the bladder

Case 2 An army officer born in 1932 History of epidemic hepatitis at 18 When he was 24 a routine study revealed a tumour of the anterior mediastinum (Medical Department, Military Hospital, Copenhagen) At the Surgical Department D of the University Hospital, Copenhagen, thoracotomy was performed in August 1955, removing as radically as possible a tumour, the size of a closed fist, which invaded the aorta, superior vena cava, and pericardium Micr exam Thymoma or Hodgkin's disease of the thymus During the period 1955—1958 the patient received X ray therapy, a total of 34,750 r, administered to the mediastinum, both sides of the neck, and axillae (Department of Radiology, University Hospital) In 1957 he developed a severe superior vena cava syndrome treated from June 1958 to August 1962 with Dicumarol© Chlornaphazin was administered as shown in fig 1, because of itching sweating fever, and progressing lymphomas This controlled the condition so that after the operation the patient had no illnesses until haematuria occurred in 1962, when Dicumarol had been withdrawn Now a tumour was found as illustrated in fig 1 Cystotomy and electrocoagulation of the tumour were performed in the surgical department of the Finsen Institute Micr exam Solid carcinoma However only 4 months later he again had profuse bleeding caused by a recurrence of the tumour which occluded both ureteral orifices Operation in

the Copenhagen County Hospital Dept D necessitated uretero cutaneostomy as the bladder was completely filled with a large tumour The patient died 2 months later in his home in a state of increasing cachexia despite a tolerable renal function

Case summary A young man with Hodgkin s disease which, after heavy X ray irradiation exclusively to the chest, neck and axillae was treated for 6 years with chlornaphazin in a total dose of 176 g The patient developed a carcinoma of the bladder which led to death in one year

Case 3 A female musician born in 1918 Two deliveries (1939 and 1948) Appendicectomy in 1958 epidemic hepatitis in 1946

In January 1956 the patient developed cervical lymphoma sweating itching and fever Biopsy revealed Hodgkin s disease In May 1957 a mediastinal tumour was diagnosed and treated in New Zealand with X ray therapy In the course of the subsequent year she received further radiation (Department of Radiology University Hospital Copenhagen) almost 6 000 r to the mediastinum neck and axillae At the same time she was treated with chlornaphazin a total of 149 5 g in 5 years with a good effect upon fatigue sweating and generalized itching In 1962 when she was again in New Zealand she developed haematuria and a bluish tumour measuring 2 cm was found just within the internal urethral orifice (cf fig 1) projecting into the vagina as well as bladder in which there were also 2 papillomas Biopsy failed and the lesion was interpreted as a manifestation of Hodgkin s disease Treated with X ray irradiation of a single field 10 × 12 cm direct from the anterior aspect 4 mV Tumour dose about 2 000 r The tumour yielded but subsequent cystoscopy within the next few months revealed severe diffuse cystitis which was difficult to explain on the basis of the X ray dose which had been received The patient herself administered her chlornaphazin while in New Zealand in the cumulation dose shown in fig 1 after the tumour had been demonstrated and treated by X rays

After she returned to Denmark in the spring 1963 she was distressed by constant pain behind the symphysis and incessant voiding of minimal quantities of haemorrhagic urine She had severe haemorrhagic anaemia, but the creatinine was normal The bladder capacity was small and cystoscopy (in Dept D Copenhagen County Hospital) revealed severe diffuse cystitis and bladder tumour The bladder was removed (Dr T Cl Gertz) The tumour measured 6 cm in diameter Microscopic examination showed adenomatous and solid carcinoma

Case summary A youngish woman with Hodgkin's disease was treated, after moderate doses of X rays to the mediastinum neck, and axillae, with chlornaphazin a total dose of 149 5 g in 5 years She then developed a tumour of the bladder which, without biopsy, was interpreted as a lymphogranulomatous focus The treatment with chlornaphazin was continued through the subsequent 2 years an additional dose of 55 g, after which she exhibited severe diffuse cystitis and bladder carcinoma

Discussion

Cancer of the bladder is one of the forms of cancer which have been best elucidated pathogenetically As early as the end of last century, it was realized that workers engaged on the manufacturing of certain dyes were quite particularly apt to develop cancer of the bladder (11) This applied whether they were engaged on aniline (so-called aniline cancer) or, as was found later, derivatives thereof (2 naphthylamine 2 amino 1 naphthol, benzidine and 4 aminobiphenyl)

In 1938 it was demonstrated by Hueper et al (7) that 2 naphthylamine may induce cancer of the bladder in dogs but if an isolated pouch of the bladder was formed which was never in touch with the urine, cancer would never develop in this site (13) In 1952 Bonser et al (1) found that inter alia 2 amino 1 naphthol implanted into the urinary bladder of mice

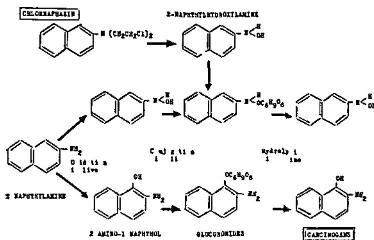


Fig 2 Chart illustrating the metabolic conversion of 2 naphthylamine into carcinogenic compounds and the presumed place of chlornaphazin in the process

had a pronounced carcinogenic effect It was now discovered that it was not aniline itself which was carcinogenic and that "aniline cancer" must be due to amines containing the aniline Strangely enough, 2-naphthylamine, which when administered orally to dogs produces cancer only of the bladder and not of the gastrointestinal tract, does not induce bladder cancer in rats, rabbits, or monkeys The explanation is that 2-naphthylamine *per se* is apparently not carcinogenic, but is converted in the body to a highly carcinogenic metabolite which forms only to a slight extent in the rat and rabbit, but to a marked extent in the dog These amines thus appear to be specific *inducers of cancer of the bladder*

2-naphthylamine, which is easily absorbed from the intestine, skin, and lungs, is oxidized in the liver to 2-naphthylhydroxylamine or 2-amino-1-naphthol (fig 2) which again is immediately conjugated with glucuronate This results in water-soluble compounds which are not carcinogenic, but are excreted mainly in the urine If the urine, as in the dog and in man, has a high β-glucuronidase activity, hydrolysis of the conjugates will now again, but this time in the urine, form 2-naphthylhydroxylamine and 2-amino-1-naphthol (2) both of which are strong carcinogens

Chlornaphazin, which is closely related to 2-naphthylamine (fig 2), apparently follows the same metabolic course In other words, after hydroxylation and conjugation in the liver, the agent will be excreted in the urine, and in the urine carcinogenic compounds will be formed under the influence of β glucuronidase (which has a pH optimum around 5 0) The reason why cancer develops in the bladder, and not in the ureter or in the kidney, is presumably that the urine rapidly passes down into the bladder where it often stays for hours This affords the β glucuronidase ample time to act upon *the conjugates, and thus the carcinogenic* compounds are allowed, in a fairly high concentration, ample time to act upon the bladder mucosa

Chievitz and Thiede (5) have briefly reported on 2 patients with polycythaemia vera who had bladder carcinoma, but without realizing that chlornaphazin must be highly conducive to a bladder carcinoma One of these patients had received chlornaphazin, 300—400 mg daily, for about 2½ years, and the other patient had received chlornaphazin intermittently for a similar period

From fig 1 it will be seen that in the present 3 cases the bladder carcinoma arose after chlornaphazin medication for 10, 6, and 5 years respectively The individual doses ranged from 100 mg weekly to 600 mg daily The total dose before the cancer was detected was of the same order in all 3 cases i e 156, 176, and 150 g Case 1 suffered from severe polycythaemia which, however, had been easily controlled with chlornaphazin When she developed her bladder carcinoma she was 67 years of age, but otherwise in good health Cases 2 and 3 were suffering from Hodgkin s disease When case 2 at the age of 30, developed a bladder carcinoma his Hodgkin s disease had been known for 7 years, but at the time he was nevertheless in a tolerable general condition Case 3 developed her bladder carcinoma at the age of 43 five years after the first manifestation of Hodgkin s disease and she too was in a fairly good general condition

In all 3 cases chlornaphazin had had an excellent therapeutic effect However — *according to our present stage of* knowledge — the polycythaemia might have been treated with less dangerous drugs such as busulphan chlorambucil, or possibly P^{32}, while in the two cases of *Hodgkin s disease it might perhaps have* been more difficult to obtain the corresponding results by other means, chlornaphazin had a favourable effect, not least on the itching which was severe in both cases To-day, *other (and apparently* less dangerous drugs) are available e g mechlorethamine cyclophosphamide and vincaleucoblastine Polycythaemia vera and Hodgkin s disease have so far been the main indications *for chlornaphazin* Since the course of not only polycythaemia vera but also often of Hodgkin s disease may be fairly benign and extend over many years it must be considered that despite the favourable effect of chlornaphazin upon *these intrinsically serious* conditions, the risk of developing cancer of the bladder is so great that in the future the drug should not be used

Summary

It is stressed that chlornaphazin has often had a relatively good effect in the treatment of Hodgkin s disease and polycythaemia vera

The author reports 3 cases in which cancer of the bladder developed after chlornaphazin medication The doses are reported in detail Further cases of bladder tumours in patients treated with chlornaphazin may be expected in the near future

Lastly it is briefly explained that in *view of present knowledge regarding the* metabolism of related substances, chlornaphazin must be considered particularly prone to induce cancer of the bladder

A warning is sounded against its future use

Acknowledgement

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The Relation Between Hypopotassaemia and Alkalosis During Administration of Polythiazide and Chlorthalidone

By

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In those treating hypertensive or oedematous patients with the modern oral diuretics the frequent occurrence of hypopotassaemia is well known, and most manufacturers recommend the addition of KCl The cause of the hypopotassaemia was originally considered to be a large urinary output of potassium, as occurs during the administration of carboan hydrase inhibitors The thiazides and chlorthalidone however, give only a modest increase in potassium excretion through the kidneys and if additional KCl is given there is no net loss of potassium at all (12) The metabolic alkalosis which also develops during the administration of diureties has not attracted much attention in this connection Animal studies have shown that the ratio of intracellular to extracellular potassium is increased in alkalosis (6 14) and the same was found in man by Siggaard Andersen (15) and Bergstrom (4) Increased serum potassium during acidosis is known both from animal experiments and from clinical studies such as those of Young et al (22) in prolonged hypercapnia and in newborn infants (18) In view of these findings it seemed to us worth while to study the relation between the alkalosis and hypopotassaemia in a series of patients getting chlorthalidone and polythiazide, and in some control subjects

Material

Sixty patients and 5 normal controls were studied Fourty five of the patients and one of the controls were women In 40 of the patients the indication for the diuretic therapy was hypertension Twenty of them had oedema of various origins mainly cardiac insufficiency Fourty four patients received chlorthalidone (Hygroton®) usually 100 mg daily 7 received polythiazide (Renese®, Pfizer AB, Stockholm) 1 mg daily and 7 received various other thiazide compounds The patients varied in age between 40 and 80 years and the controls between 22 and 44 years

Methods

Base excess is the metabolic variable in the acid base balance and expresses in mEq/l the surplus of base in the blood It was measured according to Astrup et al (2) Serum potassium (K_S^+) was measured with an Eppendorf flamephotometer by the Department of Clinical Chemistry which also performed

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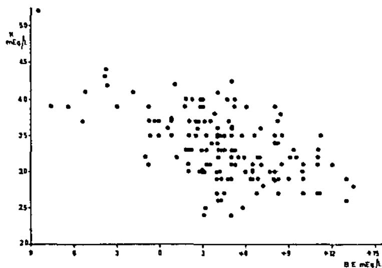


Fig. 1. Relation between serum potassium and base excess in 60 patients and 5 controls.

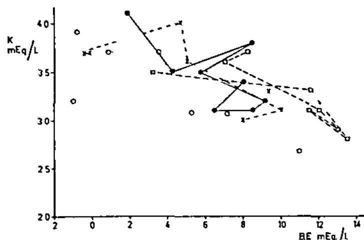


Fig. 2. Relation between serum potassium and base excess in individual controls during polythiazide administration.
The first sample in the left hand corner was taken before commencement of 1 mg daily of polythiazide except in case 1.
Case 1. Polythiazide daily for 14 days. First sample after 3 days: B.E. + 8.2. Note normalisation of the alkalosis which began after 10 days.
Case 2. Polythiazide daily for 7 days.
Case 3. Polythiazide daily for 7 days. Additional KCl 3 g daily.
Case 4. Polythiazide daily for 6 days.

the titration for chlorides according to Scribner (13).

A preliminary study showed the importance of careful sampling technique for the potassium analyses. Attention was paid to the errors as mentioned by Bergstrom and Hultman (3). In addition it was found that the values could increase almost twofold when the blood was aspirated into syringes. Therefore in all cases the blood was allowed to flow freely into heparinized tubes.

Total body potassium was measured from the radioactivity of the naturally occurring radioactive isotope ^{40}K, 0.0119 % of the naturally occurring potassium is in the form of ^{40}K. These analyses were carried out in the Department of Radiophysics by Professor K. Lidén, Ph. D.

Results

In fig. 1 all the K_S^+ values measured are plotted against base excess (B.E.). It will be seen that the higher the base excess, or in other words, the more pronounced the metabolic alkalosis, the lower the serum potassium, but there is a considerable variation. To a large extent this is due to individual differences, as seen from fig. 2. This shows how alkalosis and hypopotassaemia was induced in 4 controls by the administration of 1 mg polythiazide daily. The slope of the curves shows no difference and the *coefficient* of regression (r) is between 0.6 and 0.8.

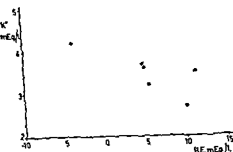


Fig 3 Relation between serum potassium and base excess in patients and controls receiving polythiazide or chlorthalidone less than 3 weeks
$K_S^+ = 3.9 - 0.10$ B E $r = 0.7$ $n = 19$
$P < 0.001$
● No KCl administration × 3 g KCl daily

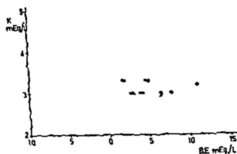


Fig 4 Relation between serum potassium and base excess in patients receiving polythiazide or chlorthalidone more than 3 weeks
$K_S^+ = 3.8 - 0.08$ B E $r = 0.5$ $n = 44$
$P < 0.01$
● No additional KCl × 3 g KCl daily

The relation between K_S^+ values and B E in 10 untreated patients with hypertension and in the 5 controls before onset of therapy showed that the slope of the curve was again the same but as most values were around B E 0 no significant correlation could be demonstrated The mean K_S^+ value in the untreated group was 3.8 mEq/l (range 3.2 to 4.3) which agrees with the normal value and range given by the Department of Clinical Chemistry

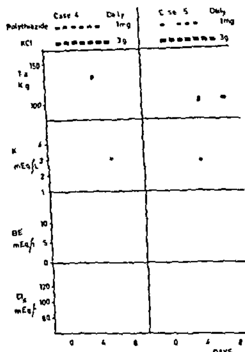


Fig 5 Effect of polythiazide administration on total potassium serum potassium base excess and serum chlorides Normal controls

It was observed that B E increased rather rapidly after a day or two when either polythiazide or chlorthalidone was administered After about 10 days B E began to return to normal As a consequence the material has been divided into two groups, one treated less than 3 weeks and one more than 3 weeks The mean B E was + 6.9 mEq/l in the former groups against only + 3.4 in the latter The results are plotted in figs 3 and 4 Here only one measurement is included from each individual which allows a calculation of the significance of the correlation This correlation is statistically significant both in those treated less than 3 weeks and in those treated more than 3 weeks The regression line for both groups together is $K_S^+ = 3.48 - 0.05$ B E ± 0.37, $r = 0.5$, $n = 63$ $P < 0.001$

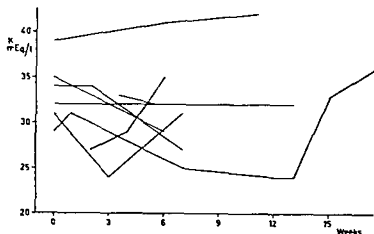


Fig 6 Variation in serum potassium during polythiazide and chlorthalidone therapy and ammonium chloride administration From time 0 3 g ammonium chloride daily was presented

In some patients supplementary KCl was given and as this could influence the results these cases are marked with crosses It will be seen that the addition of 3 g KCl daily did not influence the K_S^+/B E relationship This may also be observed in fig 2 where case no 3 (the dotted line) received supplementary KCl and in spite of this showed no higher K_S^+ than the other cases Also when case no 4 obtained additional KCl his K_S^+ was no higher than when only polythiazide was given

In two of the controls 1 mg of polythiazide and 3 g KCl were given daily, and besides K_S^+ and B E also Cl_S^- and total body potassium was measured It will be seen from fig 5 that although these cases developed a rather pronounced alkalosis and hypopotassaemia and a fall in Cl_S^-, the total body potassium remained unchanged As a consequence the ratio between extracellular and intracellular potassium dropped

Finally in a series of 8 of the patients receiving polythiazide 3 g of ammonium chloride was prescribed daily in order to compensate for the alkalosis In most cases B E became normal and K_S^+ increased Due to the rather irregular behaviour in the K_S^+/B E ratio, K_S^+ has to be shown in relation to time only

Discussion

Fenn and Cobb (6) studying isolated frog muscles found that the ratio K_S/K_C was elevated in acidosis This was later found to have general validity and is of clinical importance as it explains the high K_S^+ found in respiratory insufficiency with acidosis (22) and during the acidosis of asphyciated newborn infants (18) Conversely the ratio decreases in alkalosis as shown by Scribner et al (14) in dogs and by Siggaard Andersen (15) also in dogs, whether the alkalosis be of respiratory or metabolic origin From these studies it could be assumed that the alkalosis known to occur during therapy with diuretics could cause the hypopotassaemia often observed in this connection The present study confirmed this as the correlation between serum potassium and base excess was statistically highly significant Sandoe and Olesen (12) found a metabolic alkalosis, i e a standard bicarbonate higher than 25 6 mEq/l, in 50 % of their 18 cases This would correspond to a B E of + 4 mEq/l, and 53 % of the measurements shown in fig 1 are above this value These authors found some reduction in the frequence of hypopotassaemia after supplementary KCl administration, whereas the frequence of metabolic alkalosis was

less affected They therefore concluded that the alkalosis and hypopotassaemia were not closely related to each other By contrast the present investigation has shown a strong correlation between the hypopotassaemia and the metabolic alkalosis, neither of which could in our experiments be compensated by the addition of KCl

The alkalosis and consequently also the hypopotassaemia is more pronounced at the onset of polythiazide and chlorthalidone therapy No significant difference could be observed between those receiving polythiazide and those getting chlorthalidone Nor was there any difference between the patients with hypertension and those with oedema The degree of alkalosis may seem surprising, going as it does to + 10 mEq/l or more after 8 to 10 days of therapy It is, however no more than observed in several cases receiving mercury diuretics (Rooth, unpublished)

It is well known that mercury diuretics are more effective if the patient is made acidotic initially by the administration of ammonium chloride According to Reutter and Schaub (9) and Wilson (21) this should not affect the modern oral diuretics The diuretic effect in the 8 cases where we gave ammonium chloride could not be evaluated as these patients already were rid of oedema but an indication that it may be worth while to try ammonium chloride during polythiazide therapy was obtained in an additional case

A woman 51 years of age with a severe aortic stenosis and insufficiency had had signs of left heart failure for several years and had been hospitalized 3 times within the last 6 months. Her situation was desperate none of various diuretics including mercury diuretics and polythiazide having any effect On 2 mg of polythiazide her diureses was only 750 ml. After 10 g of ammonium chloride the diuresis increased to 2,400 ml A few days later an almost as good improvement was again observed She died a month later

Recent literature on thiazide and chlorthalidone therapy is almost unanimous that KCl should be given Most of these statements are based on a slightly increased potassium elimination and on a frequent finding of hypopotassaemia However, Lassen (8) says that only rarely are clinical signs of hypopotassaemia present and there is a risk in giving supplementary potassium to patients with kidney insufficiency Sorcini and Montervino (16), Strata and Preis (17) seldom observed hypopotassaemia or other disturbances of the blood electrolytes Andresen (1) found hypopotassaemia (3 5 mEq/l) in only 1 out of 13 cases studied with cardiac oedema, but in all of 6 cases with hepatic or renal oedema Varnaukas and Schröder (19) found hypopotassaemia in 9 out of 31 patients with hypertension like those of Andresen taking chlorthalidone Three of these patients received in addition 2 or 3 g KCl daily According to Weller (20) the risk of hypopotassaemia is overestimated Whether giving supplementary KCl or not we observed signs of hypopotassaemia in the form of general muscular weakness in 3 instances during these studies 2 of them being controls The addition of ammonium chloride promptly abolished these signs in the patient

We have found only two papers giving detailed figures for K_s^+ during thiazide therapy when supplementary KCl was given as against when it was withheld Galskov (7) found that the addition of 0 6 g of KCl daily was without effect whereas the mean K_s^+ did not drop in 10 patients receiving 1 g KCl daily nor

in 8 patients receiving 1 6 g KCl daily Sandoe and Olesen found a decrease in the frequency of hypopotassaemia when they gave 3 g KCl daily In both groups they had 18 patients and they found hypopotassaemia in 39 % of those not taking KCl and 11 % of those taking KCl This difference is almost significant They call values less than 3 6 mEq/l hypopotassaemia Their high level is probably associated with the sampling technique It may be argued that the results of Sandoe and Olesen are not significant, but those of Galskov are It is improbable that different thiazides should have different effect, and we cannot explain the difference in results The present results in this respect are, however, so convincing that we have now refrained from giving supplementary KCl to our patients during thiazide therapy They appreciate the reduction in the daily intake of tablets and moreover KCl often gives abdominal pains When the patients show signs of hypopotassaemia is does not suffice to give them 3 g KCl daily If the treatment of the diuretic cannot be discontinued it may be best to give ammonium chloride possibly supplemented with KCl if the symptoms persist

Sandoe and Olesen in doing metabolic balance studies found a mean total loss of 4 5 g of potassium during the first week of cyclopenthiazide therapy After the addition of KCl 3 g daily no net loss of potassium occurred These patients had oedema, and the greater the weight loss the greater the potassium loss In patients with hypertension the total potassium loss is probably less Delahunt (5), who gave large amounts of polythiazide to dogs for 6 months found no decrease in the potassium content of their skeletal muscle A recalculation of the data of Rooth et al (11) showed a correlation between the intracellular potassium concentration and the base excess, in normal blood $K_S^+ = 102 + 2\,0$ B E, $r = 0\,7$, $n = 13$, $P < 0\,01$ Given sufficient KCl the total body potassium content would conceivably increase in alkalosis, however, we found no change in total potassium in the two controls receiving additional KCl These two cases also differ from the experience of Sandoe and Olesen in that they got a pronounced hypochloraemia in spite of KCl administration

Summary

Both in 60 patients and in 5 control subjects a highly significant relation was established between the hypopotassaemia and the metabolic alkalosis induced by polythiazide or by chlorthalidone

No effect on serum potassium or alkalosis was observed either in the patients or in three of the controls when in addition 3 g KCl was given daily

Acknowledgements

We are grateful to Professor C G Holmberg Department of Clinical Chemistry for the potassium and chloride analysis to the medical students who served as controls and to Miss Vivi Ann Nilsson for technical assistance

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Effects of Guanethidine on Renal Function

By

A M Abrahamsen, S Humerfelt and H Sigstad

In an earlier investigation we studied the degree to which hydrochlorothiazide accentuates the hypotensive effect of guanethidine (1) The purpose of this investigation has been to study the effects of guanethidine on renal function

Brest et al (3) and Mertz (7) have shown that there is a reduction in renal blood flow (PAH clearance) and glomerular filtration (inulin clearance) after intravenous infusion of guanethidine A similar response is found after oral treatment with the drug (2 5 8) Guanethidine administration impairs the glomerular filtration rate probably because the slight reduction in renal vascular resistance that accompanies the use of the drug is insufficient to maintain blood flow and filtration pressure in the presence of the marked reduction in blood pressure (8) The changes in renal function are probably related to reduction in blood pressure rather than to any specific harmful effect of guanethidine on the kidney (8)

Material

The material consisted of 12 hypertensive patients, 8 women and 4 men (table I) The age varied from 38 to 62 years with an average age of 52 6 years Retinal changes, classified as K W & B III and IV were found in 6 patients Left ventricular hypertrophy pattern on ECG was found in 7 patients 4 of whom showed a heart volume above 600 ml/m² The rest showed a heart volume according to Jonsell s formula within the range of the normal variation The average heart volume index of the total series was 488 ml/m²

Six patients had proteinuria on admission to hospital transient in two The serum creatinine varied from 1 0 to 3 1 mg/100 ml in 5 patients $\geq$ 1 6 mg/100 ml Six patients showed negative findings on urography, in one a small stone was found in the left kidney, one patient showed a slight dilatation of the right ureter otherwise no abnormalities were found on urography

Methods

Routine renal function tests urine analyses and X ray investigations of the heart including electrocardiographic investigations were carried out on all patients The patients were treated with bed rest and a low salt diet for several days before the trial

The inulin and PAH clearances were measured before and after infusion of guanethidine ((Ismelin©) CIBA Ltd Kobro & Co Oslo) in the lying position The method used follows the principles given by Goldring and Chasis (6) In only one patient (no 2) were there only 2 periods before and 2 after the infusion In all the others 5—6 clearance periods in all were used PAH was measured by the method of Finkelstein et al (4) inulin

Submitted for publication December 18 1963

Table I Grouping of the series

Pat no Sex	Age	KW & B	ECG	Heart vol (ml/m²)	Protein uria	Creati nine	MAP (mm Hg)	
							Before infusion	After infusion
1 ♂	62	Normal	LVH	660	−	1 6	137	142
2 ♂	57	III	LVH	610	+	3 1	165	130
3 ♂	52	IV	LVH	645	+−	1 9	126	138
4 ♂	44	Normal	Normal	420	−	1 5	114	120
5 ♀	62	III	LVH	445	+−	1 4	127	116
6 ♀	62	I	Auric fibrill	455	+	1 3	127	99
7 ♀	57	III	LVH	660	+	2.2	173	160
8 ♀	53	I	LVH	390	−	1 1	137	129
9 ♀	53	III	LVH	400	+	1 6	158	133
10 ♀	50	I	Normal	425	−	1 2	172	143
11 ♀	41	III	Normal	340	−	1 3	168	173
12 ♀	38	I−II	Normal	400	−	1 0	140	124

LVH = left ventricular hypertrophy
MAP = *mean arterial pressure (diastolic pressure plus ¹/₃ of the pulse pressure)*

by Schreiner's method (9) The clearance values are calculated per 1 73 m² body surface

In 4 subjects the investigations were under taken on the same day as the guanethidine infusion In 8 cases the first clearance studies were performed 3 to 5 days before the guanethidine infusion and in the subsequent clearance periods The intravenous infusion of guanethidine was given in the course of 15 minutes The dose was 0 25 mg/kg body weight dissolved in 100 ml 5 % glucose

The blood pressure was measured by auscultation at regular short intervals in all clearance periods before and after the infusion The mean arterial pressure was estimated (tables I and II)

The cardiac output was estimated by the dye dilution technique before and after the guanethidine infusion using Evans blue and the Cambridge dye-dilution recorder Mark II

Results

The mean arterial pressure showed a significant fall from an average of 145 mm to 133 mm Hg ($0\ 02 < P < 0\ 05$) In 5 subjects the fall was considerable while a slight fall was noted in 3 However, in 4 a slight increase of mean arterial pressure was recorded

The renal plasma flow (PAH) showed only an insignificant fall from an average of 329 to 316 ml/min In 2 cases (nos 2, 7) the renal plasma flow was markedly reduced (below 175 ml/min) and a further decrease was noted after the guanethidine infusion In 7 subjects PAH clearance was estimated to be between 225 and 375 ml/min before the infusion and in only 4 of these was a further reduction recorded In 3 subjects (nos 4, 11, 12) the renal plasma flow was normal with a slight reduction after the infusion in 2

The glomerular filtration rate (inulin) was normal in 4 patients, a slight reduction was noted in 2 In all the others the inulin clearance varied from 89 to 23 ml/min Reduction of the glomerular filtration rate was noted in only 2 patients (nos 3, 6) after the guanethidine infusion while the rest showed a slight increase or remained constant On the

Table II Effect of intravenous guanethidine on mean arterial pressure, PAH and inulin clearances, and cardiac output

	Before	After	Difference
Mean arterial pressure (mm Hg)			
$\bar{x} \pm$ SE	145 ± 6 0	133 ± 5 7	t test 2 49
SD	21	20	0 02 < P < 0 05
PAH clearance (ml/min/1 73 m²)			
$\bar{x} \pm$ SE	329 ± 40	316 ± 46	
SD	139	160	
Inulin clearance (ml/min/1 73 m²)			
$\bar{x} \pm$ SE	82 ± 9	88 ± 12	
SD	30	42	
Cardiac output (l/min)			
$\bar{x} \pm$ SE	6 0 ± 0 6	5 6 ± 0 7	
SD	1 6	1 9	

average there was an increase in inulin clearance (not significant, see table II) No correlation was found between the blood pressure difference and the difference in PAH and inulin clearances

In 7 out of 12 patients (nos 1 2, 3 4 8, 10 12) the cardiac output was estimated An insignificant reduction was recorded, being on an average 0 4 l/min (table II), in 4 a decrease and in 3 an increase were noted

Side effects

No serious side-effects were seen The investigations were performed in the recumbent position and the patients were not allowed to leave the bed until several hours afterwards No increase of blood urea or clinical exacerbation of the illness was seen in the following days

Discussion

The results presented in table II show marked variations in all parameters A significant difference between the values before and after the guanethidine infusion is found only for the mean arterial bl[...] pressure

The difference is only 12 mm Hg [...] a series previously published, the fal[...] the mean arterial pressure was 49 [...] Hg following the same dosage gi[...] intravenously This difference may [...] due to the more serious cases in the p[...] ent material (cf the serum creati[...] values)

Clearance studies as such are ra[...] disturbing to the patients and this [...] also explain the small blood pressure [...] crease during the clearance peri[...] Therefore the blood pres ure decr[...] during the clearance periods does [...] completely correspond to the maxim[...] blood pressure fall following the gu[...] thidine infusion

This may also explain the lack of [...] relation between the renal plasma [...] and glomerular filtration rate and [...] decrease in blood pressure After [...] administration of the drug Richar[...] and Wyso (8) found a significant re[...] tion in mean arterial pressure from [...] to 129 mm Hg resulting in a signif[...]

reduction in inulin clearance, but not in the PAH clearance in a series of 14 hypertensive subjects. However, after head-up tilting at 40° a significant reduction in both clearance tests was found. Prior to treatment, the glomerular filtration rate in these hypertensive patients was about 60 % of normal, and renal plasma flow was reduced even further, to 42 % of normal. Bartorelli et al. (2) observed a proportional reduction of both renal function tests after 8—30 days of oral administration of the drug. These effects were more pronounced in the standing position.

Ford et al. (5) noted a decrease in glomerular filtration rate and renal plasma flow in 6 of the 10 patients tested following 3 weeks of guanethidine therapy.

Mertz (7) in a series of 15 adults without any disorders of renal function noted a significant decrease of urine flow and inulin and PAH clearances after intravenous administration of 20 mg guanethidine.

Brest et al. (3) also noted a reduction in the same tests after an intravenous infusion of guanethidine in a small series of 8 patients using the same dose as in our material.

Of the series hitherto published very few can be compared with the present series. Only the series of Richardson and Wyso (8) shows a greater reduction in the renal function tests prior to treatment than this material. The series of Brest et al. (3), on the other hand, shows figures indicating a slightly better renal blood flow and glomerular filtration rate.

In general the results of renal function studies of this type will depend upon the seriousness of the hypertensive state. In this material no serious side-effects were observed during or after the clearance periods.

Conclusion and summary

The purpose of this investigation was to study the influence of guanethidine on renal function. Intravenous infusion of guanethidine, 0.25 mg/kg body weight dissolved in 100 ml 5 % glucose, was given in the course of 15 minutes. The blood pressure was measured by auscultation at short regular intervals in all clearance periods before and after the infusion.

The material consisted of 12 patients, 8 women and 4 men, with an average age of 52.6 years. Six patients had proteinuria on admission to hospital, transient in two of them. The serum creatinine varied from 1.0 to 3.1 mg/100 ml.

The mean arterial pressure showed on an average a significant fall from 145 mm to 133 mm Hg. The renal plasma flow (PAH) showed only an insignificant fall from an average of 329 to 316 ml/min/1.73 m. In 9 subjects the PAH clearance was reduced before the infusion, in only 6 of these was a further reduction recorded. The glomerular filtration rate (inulin) showed an insignificant increase.

No correlation was found between the difference in the blood pressure and the difference in PAH or inulin clearance. No serious side effects were seen.

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The Effect of Carotid Occlusion and Central Vagal Stimulation on the Free Fatty Acids of Plasma and the Blood Pressure in the Dog[1]

By

SVEN FROBERG and LARS ORO

The role of the sympathetic nervous system in the mobilization of the free fatty acids of plasma (FFA) from adipose tissue in man as well as in dog, has become evident during recent years (14) Infusions of catecholamines norepinephrine and epinephrine elevate not only the blood pressure but also the plasma FFA concentration (9 10 13 17) Ganglionic blocking agents such as hexamethonium decrease the plasma FFA concentration as well as the blood pressure in dogs (13) During many conditions with an increased activity in the sympathetic nervous system there is also an increased plasma FFA concentration e g during mental stress (3) prolonged exercise (2 6 7), respiratory acidosis (20) and hypoxia (21) and also during hypoglycemia induced by insulin 1 However the exact mechanism of the FFA mobilization caused by the sympathetic nervous system is not known

It is well established that baroceptor reflexes are of importance for the regulation of the blood pressure (4 18 19 24) It was recently reported that the plasma FFA concentration increased during tilting in normal men but not in patients with so called autonomic insufficiency (12, 14) The results suggested that the baroceptor reflexes also were of importance for the FFA mobilization

This investigation was performed to study the possible role of baroceptor reflexes in FFA metabolism by means of carotid occlusion and central vagal stimulation in the dog The effect of carotid occlusion and central vagal stimulation on the blood pressure and the plasma FFA concentration was compared with the effect of different doses of norepinephrine and epinephrine infused intravenously

Methods

Experimental

In all series of experiments dogs weighing between 14—24 kg were used In the morning after fasting overnight they were anesthetized

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[1] A report was presented before the XI Scand Physiol Congr Copenhagen August 1963

Table I Effect of carotid occlusion and central vagal stimulation on the blood pressure and the concentration of free fatty acids of plasma The figures give the mean values and SE of mean and are calculated from the changes in the individual dogs

	Initial rise of mean blood pressure (mm Hg)		Rise of FFA concentration after 30 min (mEq/l)	
	Period I	Period II	Period I	Period II
Carotid occlusion (8 dogs)	[2]69 ± 9	[2]55 ± 7	[2]0.14 ± 0.03	[1]0.11 ± 0.04
Central vagal stimulation (6 dogs)	[1]53 ± 6	[2]61 ± 7	0.01 ± 0.01	0.00 ± 0.02

[1] Statistical significance $p < 0.05$
[2] Statistical significance $p < 0.01$

with Nembutal® (Abbott) 30 mg/kg body weight Blood pressure was measured continuously with an Elema Schonander pressure transducer (EMT 490 A) from a teflon catheter inserted into one femoral or brachial artery The blood pressure transducer was filled with saline and no heparin was introduced into the animal

In the *first* series of experiments the two common carotid arteries were dissected free They were clamped off, at the level of the thyroid gland, during two periods The periods were of 30 minutes duration and 60 minutes apart In three experiments the dogs were not killed but kept alive, and the day after the experiments they behaved quite normally

In the *second* series of experiments the vagus nerves were dissected free and cut in the neck The two central ends of the nerves were stimulated electrically for two periods, each of 30 minutes duration and 40 minutes apart The stimulator gave square impulses 35 per second and of 7 msec duration The strength was in the range from 10—20 volts so as to produce a maximal rise of the blood pressure The stimulation caused apnea Therefore the dogs were given artifical respiration with air during the whole experiment The respiratory speed and volume were adjusted at the beginning of the experiment, before the stimulation so that the dogs started to breathe spontaneously after 5—15 seconds if the ventilation was interrupted

In the *third* series of experiments different doses of norepinephrine (1 base) and epinephrine were infused intravenously at a constant rate during thirty minutes Two or three different doses were given in each experiment At least 60 minutes elapsed between the infusions, so that the FFA concentration had fallen to the initial level before each infusion

Analytical The free fatty acids of plasma (FFA) were determined by the method of Dole (8)

Results

The effect of carotid occlusion on the blood pressure and on the concentration of free fatty acids of plasma

When the two common carotid arteries were clamped off there was an immediate rise of the mean blood pressure in all dogs (fig 1 and table I) The mean rise during the first period was from *127 to 196 mm Hg and during the second period* from 120 to 175 mm Hg It is evident from the figure that after this initial rise the blood pressure remained high throughout the occlusion

The mean plasma FFA concentration increased from 0.33 to 0.46 mEq/l during the first period and from 0.37 to 0.47 mEq/l during the second period (fig 1 and table I)

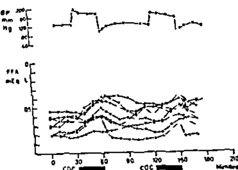


Fig 1 The effect of carotid occlusion on the mean blood pressure (BP mean value) and the arterial concentration of free fatty acids of plasma (FFA) in 8 dogs The two common carotid arteries were occluded during two periods (COC)

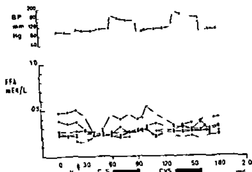


Fig 2 Effect of central vagal stimulation on the mean blood pressure (BP mean value) and the arterial concentration of free fatty acids of plasma (FFA) in 6 dogs The two vagus nerves were cut in the neck at V The central ends were stimulated during two periods (CVS) Artificial respiration with air was given during the experiments

The effect of central vagal stimulation on the blood pressure and on the concentration of free fatty acids of plasma

Electrical stimulation of the central ends of the vagus nerves increased the mean blood pressure during the two periods of stimulation (fig 2 and table I) The initial rise during the first period was from 110 to 163 mm Hg and during the second period from 115 to 176 mm Hg The mean plasma FFA concentration was unchanged during the first as well as the second period fig 2 and table I)

The effect of different doses of norepinephrine on the blood pressure and on the concentration of free fatty acids of plasma

Norepinephrine was infused i v at a constant rate during periods of thirty minutes When 0 04 to 0 08 μg/kg/min was given there was an increase of the plasma FFA concentration in all experiments while the mean blood pressure was unchanged (fig 3) Norepinephrine in doses from 0 3 to 0 6 μg/kg/min produced a more marked rise of the FFA concentration With these doses the mean blood pressure also increased (fig 3)

The effect of different doses of epinephrine on the blood pressure and on the concentration of free fatty acids of plasma

Epinephrine was infused i v at a constant rate during 30 minutes Doses from 0 04 to 0 08 μg/kg/min caused an increase of the plasma FFA concentration while the mean blood pressure decreased (fig 4) With higher doses of epinephrine, 0 30 to 0 60 μg/kg/min, there was a more marked increase of the plasma FFA concentration The mean blood pressure was also elevated by these doses (fig 4)

Discussion

Occlusion of the common carotid arteries produces an inhibition of nerve impulses from the pressor sensitive structures in the carotid sinus to the so-called depressor "centrum in medulla oblongata Thereby an increased activity in the

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The mean plasma FFA concentration increased from 0.33 to 0.46 mEq/l during the first period and from 0.37 to 0.47 mEq/l during the second period (fig 1 and table I)

in the plasma FFA concentration and blood pressure was therefore compared with the effect of different doses of catecholamines infused i v on the same parameters Except that norepinephrine seemed a little more effective in elevating the FFA concentration there was no major difference between norepinephrine and epinephrine in this respect Doses of norepinephrine from 0 04 to 0 08 μg/kg/min increased only the FFA concentration but not the blood pressure These doses of norepinephrine also caused a more marked rise of the FFA concentration than was produced by carotid occlusion To reproduce the effect of carotid occlusion on the blood pressure higher doses of norepinephrine 0 3 to 0 6 μg/kg/min, had to be given which caused an almost tenfold rise of the plasma FFA concentration This comparison suggested that carotid occlusion in contrast to a norepinephrine infusion produced vasoconstriction with little increase in FFA mobilization The recent finding that carotid occlusion in dog produced reflex antidiuresis suggested a release of antidiuretic hormone (23) It has also been found that oxytocin as well as vasopressin in the dog decreases the plasma FFA concentration (11) Thus the possibility cannot be excluded that during carotid occlusion hormones were released which inhibited FFA mobilization

The sympathetic nervous system was therefore also activated in another way by means of central vagal stimulation When somatic afferents including the vagus nerves are electrically stimulated the circulatory changes depend on the type of stimulus 15) In this investigation only a strong stimulus was used known to cause vasoconstriction and a blood pressure rise Despite the marked blood pressure rise the vagal stimulation did not increase the plasma FFA concentration at all Like the foregoing results these findings suggested that sympathetic vasoconstrictor nerves can be activated in the dog without an enhanced FFA mobilization

From the results it was evident that although the rise of FFA produced by carotid occlusion was small it was statistically significant, whereas the central vagal stimulation did not change the FFA concentration Carotid occlusion is known to produce a cerebral anemia (5) This anemia may not be of importance for the blood pressure effect during carotid occlusion in the dog (5) However, since respiratory acidosis as well as hypoxia (20 21) has been reported to increase the FFA concentration, it is possible that an anemic hypoxia and not the baroceptor activation was the cause of the small rise of FFA during carotid occlusion

Blood flow and blood distribution are of importance for the flux and concentration of FFA (6) If a marked vasoconstriction and decreased blood flow through adipose tissue is produced, one might expect catecholamines to be less effective in enhancing FFA mobilization However, an infusion of norepinephrine during carotid occlusion also produced a marked rise of the FFA concentration (22) This seems to prove that the circulatory changes per se did not inhibit the effect on FFA of endogenous catecholamines released from peripheral sympathetic nerve endings during the baroceptor reflex activation

The present investigation therefore strongly suggested that sympathetic vasoconstrictor nerves can be activated by means of carotid occlusion and central vagal stimulation in the dog without any major mobilization of free fatty acids to plasma It is therefore possible that baroceptor reflexes are of no importance for FFA mobilization

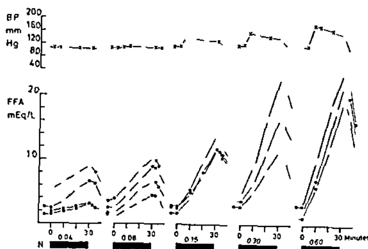


Fig 3 Effect of norepinephrine on the mean blood pressure (BP, mean value) and the arterial concentration of free fatty acids of plasma (FFA) in dogs Norepinephrine (N) was infused i v at a constant rate in doses from 0 04 to 0 60 μg/kg/min

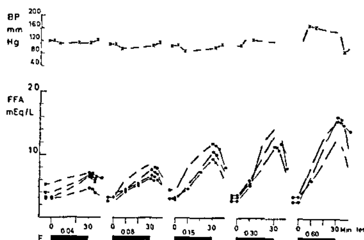


Fig 4 Effect of epinephrine on the mean blood pressure (BP mean value) and the arterial concentration of free fatty acids of plasma (FFA) *in dogs Epinephrine (E) was infused* i v at a constant rate from 0 04 to 0 60 μg/kg/min

sympathetic vasoconstrictor nerves is produced, which is considered to be the mechanism for the blood pressure rise (18, 24) According to Kaindl and von Euler (16) no increased release of catecholamines from the adrenal glands occurs when the vagus nerves are intact as in this investigation It was here found that when the carotid arteries were clamped off as long as thirty minutes the mean blood pressure was markedly elevated during the whole period It was also found that the blood-pressure rise could be reproduced during a second period of occlusion These results and the normal behaviour of the dogs the day after the experiment seems to indicate that no structures in the brain were damaged by the bilateral carotid occlusion

The current concept is that sympathetic nerve impulses are transmitted to the smooth muscles of the vessels causing vasoconstriction by means of catecholamines, probably only norepinephrine (25) Norepinephrine seems also to be of importance for FFA mobilization (14) The blood-pressure rise during carotid occlusion suggested an increased activity in the sympathetic vasoconstrictor nerves with a release of norepinephrine However, there was only a small rise *of the FFA concentration,* 0 12 mEq/l The effect of carotid occlusion

16 KAINDL, F & VON EULER U S Liberation of nor adrenaline and adrenaline from the suprarenals of the cat during carotid occlusion Amer J Physiol *166* 284 1951
17 LAURELL, S & CHRISTENSSON B Effect of a single dose of some hormones on plasma unesterified fatty acid (UFA) Acta physiol scand *44* 248 1958
18 LINDGREN P The central regulation of the autonomic nervous system with special regard to the vasomotor control Biochemistry Pharmacology and Physiology Pergamon Press Ltd London 1961 p 103
19 LUFT R & VON EULER, U S Two cases of postural hypotension showing a deficiency in release of nor-epinephrine and epinephrine J clin Invest *32* 1065 1953
20 MCELROY JR W T & SPITZER J J Mobilization of free fatty acids in dogs during respiratory acidosis J appl Physiol *16* 339 1961
21 MCELROY JR, W T & SPITZER J J Hypoxia as a stimulus for free fatty acid mobilization in dogs J appl Physiol *16* 760, 1961
22 ORO L Unpublished observation
23 PERLMUTT J U Reflex antidiuresis after occlusion of common carotid arteries in hydrated dogs Amer J Physiol *204* 197, 1963
24 UVNAS B Central cardiovascular control Handbook of physiology Section 1 Volume II 1960 p 1131
25 Adrenergic mechanisms A CIBA Foundation Symposium J & A Churchill Ltd London 1960

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Carotid occlusion as well as central vagal stimulation produced a marked rise in the mean blood pressure during two 30 minute periods The mean plasma concentration of FFA increased only slightly, but significantly, from 0 33 to 0 46 mEq/l and from 0 37 to 0 47 mEq/l during the two periods of carotid occlusion respectively When the central ends of the cut vagus nerves were stimulated, the plasma FFA concentration was unchanged To reproduce the effect of carotid occlusion and central vagal stimulation on the blood pressure, doses of norepinephrine and epinephrine were infused intravenously The requisite doses caused an almost tenfold rise of the plasma FFA concentration

The results suggested that vasoconstrictor nerves can be activated by means of baroceptor reflexes without any major mobilization of FFA in dogs

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Hypoparathyroidism and Pernicious Anaemia

By

E Ikkala M Siurala and M Viranko

Seven patients with concomitant primary hypoparathyroidism and Addisonian pernicious anaemia have been described in the literature so far (4, 6, 7, 9, 12 13) As the total number of patients with primary hypoparathyroidism published is rather small — according to Rasmussen and Reifenstein (8) about 85 — the co existence of these two diseases can scarcely be due to mere coincidence

We have observed one patient suffering from primary hypoparathyroidism and pernicious anaemia In addition, in order to study the effect on removal of the para thyroids on the functional and anatomical condition of the stomach four patients with inadequetely treated post operative hypoparathyroidism have been investigated

Case reports

The patient with idiopathic hypoparathyroidism and Addisonian pernicious anaemia

The patient was a hospital handyman born in 1932 His childhood development had been slightly slower than normal he learnt to walk at the age of 1 5 years to speak at 3 and failed twice in elementary school to gain promotion to the next form

Submitted for publication December 27 1963

He first felt pain in his limbs at the age of 4 and there were concurrently mild cramps Cramps have subsequently occurred intermittently, especially in connection with infectious diseases of which the patient had a high childhood incidence Broad tapeworm was expelled from him at the age of 11 but neither anaemia nor jaundice were established in this connection

The patient had had several episodes of anaemia jaundice and cramps in 1949—1952 and had been treated for them both by private practitioners and in hospital He had always received injections of liver preparations immediately before admission to hospital His anaemia was regarded as haemolytic on the basis of the demonstrable reticulocytosis and normoblastic bone marrow Anacidity was shown with the alcohol test meal The cramps were attributed to hypoparathyroidism Serum calcium was 5 2 mg/100 ml at its minimum and was normalised by peroral vitamin D therapy

The patient was in relatively good condition without regular treatment from 1953 to the end of 1961 Gradually increasing fatigue and cramps led to hospitalisation once again in June 1962

The patient was found to be of slight build (height 162 cm weight 46 kg) the pelage was feminine and the testes small Nothing indicative of pseudohypoparathyroidism was noted, however

Chvostek s and Trousseau s signs were positive and the QT interval was prolonged in

Table I Patients with post-operative hypoparathyroidism

Pat	Age Sex	Time of operation	Time of examination	Serum calcium (mg/100 ml)	Serum phosphorus (mg/100 ml)	The peak secretion of HCl[1] (mEq/l)	Gastric biopsy[2]	Concomitant disease
E I	51 ♀	1948	6/61	8 4	4 6	—	—	Hypothyroidism nephropathia
			6/63	10 7	4 2	53	Superficial gastritis	—
L. L.	50 ♀	1939	4/61	8 1	7 0	—	—	—
			6/63	6 5	5 8	68	Superficial with incipient atrophic gastritis	—
			9/63	11.5	5.2	—	Unchanged	—
I P	42 ♀	1951	3/59	6 4	9 3	—	—	—
			6/63	9 7	3.3	53	Superficial gastritis	Hypothyroidism
U O	57 ♂	1943	12/58	5 7	7.5	—	—	—
			9/6/63	5 4	4 9	0	Superficial gastritis	—
			20/6/63	7.2	—	40	—	—
			9/63	8 0	5 2	—	Unchanged	—

[1] Samples were drawn 30 60 and 90 minutes after administration of 10 mg/10 kg of body weight Histalog© (Lilly)
[2] 3 specimens were obtained from each patient with a Sielaff suction biopsy tube

from hospital in good condition and he continues with the dihydrotachysterol and vitamin B_{12} medication

Patients with post-operative hypoparathyroidism

Four patients with inadequately treated post-operative hypoparathyroidism were studied before and after treatment The main results are shown in table I None of these patients had any signs of disturbed vitamin B_{12} metabolism (blood picture Schilling test) One had achlorhydria which had disappeared when the re-examination was performed after treatment of the hypocalcaemia The remaining three had normal HCl secretion All four patients had distinct superficial gastritis (fig 2) Two patients were re-examined by biop after adequate treatment The gastric muco however was unchanged Vitamin A and Xylose absorption were normal in all the p tients Biopsy of the small intestine revealed normal mucosa

Discussion

Morse et al (7) described five sibli suffering from idiopathic hypoparathy idism Each of them showed symmetr partial anodontia, and a less consist association was noted with mental d



Fig 1 Gastric biopsy of the patient with primary hypoparathyroidism and pernicious anaemia Normal gastric body glands are replaced by mucus forming tubules (pseudopyloric metaplasia) Haematoxylin eosin × 80



Fig 2 Gastric biopsy of patient E I with post operative hypoparathyroidism Severe inflammatory cell infiltration is present below the surface epithelium The body gland layer is almost intact (superficial gastritis) Haematoxylin eosin ×80

ECG Serum calcium was 5 2 mg/100 ml phosphorus was 7 2 mg/100 ml and alkaline phosphatases 5 2 King Armstrong units Incipient lenticular cataract was diagnosed in the eyes Skull X ray examination displayed diffuse calcium aggregations in the basal ganglia The bone epiphyses showed transverse thin bone densities which were ascribed to *growth disturbances*

The peripheral blood picture was strongly suggestive of megaloblastic anaemia Hb 9 3 g % erythrocytes 1 93 million/mm³, PCV 31 % MCH 48 MCV 160 MCHCH 30 leukocytes 7 600 neutrophils displaying poly segmentation platelets 160 000/mm³ reticulocytes 0 8% The bone marrow was markedly megaloblastic The Schilling test was 0 % and with intrinsic factor 8 % In view of the further demonstration of reticulocytosis of 14 5 % after the Schilling test Histalog refractory achylia and total atrophy in gastric biopsy (fig 1) the condition in question could be regarded as pernicious anaemia

Although the normal result given by the Schilling test with intrinsic factor argues against malabsorption at least as the cause of anaemia vitamin A and d Xylose tolerance tests were *also performed* as well as biopsy and X ray examination of the small intestine They all gave normal results and malabsorption was *consequently ruled out*

Basal excretion of 17 OH corticoids and 17 ketosteroids and response to ACTH were also normal and nothing else indicative of adrenal insufficiency was found

The patient was considered to have idiopathic hypoparathyroidism and pernicious anaemia *Dihydrotachysterol and vitamin* B_{12} therapy was instituted It reversed the changes demonstrated and the patient became completely asymptomatic

In July 1963 the patient was readmitted to hospital for calcium balance studies A 6 4-fold increase in phosphorus excretion was established in the parathyroid hormone tolerance test and pseudohypoparathyroidism was consequently excluded However no increase in phosphaturia indicative of hypoparathyroidism was achieved in Howard s intravenous calcium tolerance test The result was nevertheless not normal phosphorus excretion being little changed Calcium retention was 45 % Control blood studies were carried out at the same time blood values were normal as were the bone marrow findings On the other hand Histalog refractory achlorhydria and complete gastric atrophy were established The patient was discharged

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L L	50 ♀	1939	4/61	8.1	7.0	–	–	–
			6/63	6.5	5.8	68	Superficial with incipient atrophic gastritis	–
			9/63	11.5	5.2	–	Unchanged	–
I P	42 ♀	1951	3/59	6.4	9.3	–	–	–
			6/63	9.7	3.3	53	Superficial gastritis	Hypothyroidism
U O	57 ♂	1943	12/58	5.7	7.5	–	–	–
			9/6/63	5.4	4.9	0	Superficial gastritis	–
			20/6/63	7.2	–	40	–	–
			9/63	8.0	5.2	–	Unchanged	–

[1] Samples were drawn 30 60 and 90 minutes after administration of 10 mg/10 kg of body weight of Histalog® (Lilly)

[2] 3 specimens were obtained from each patient with a Sielaff suction biopsy tube

from hospital in good condition and he continues with the dihydrotachysterol and vitamin B_{12} medication

Patients with post-operative hypoparathyroidism

Four patients with inadequately treated post operative hypoparathyroidism were studied before and after treatment The main results are shown in table I None of these patients had any signs of disturbed vitamin B_{12} metabolism (blood picture Schilling test) One had achlorhydria which had disappeared when the re-examination was performed after treatment of the hypocalcaemia The remaining three had normal HCl secretion All four patients had distinct superficial gastritis (fig

2) *Two patients* were re-examined by biopsy after adequate treatment The gastric mucosa *however*, was unchanged Vitamin A and d Xylose absorption were normal in all the patients Biopsy of the small intestine revealed a *normal mucosa*

Discussion

Morse et al (7) described five siblings suffering from idiopathic hypoparathyroidism Each of them showed symmetrical partial anodontia, and a less consistent association was noted with mental defi-

ciency, pernicious anaemia (in two patients), steatorrhoea and adrenal insufficiency Because the concentrations of sodium and chloride in sweat were increased, they suggested that the syndrome is a variant of mucoviscidosis Although this remained unproved, it seems clear that some genetic defect was involved in these cases This might hold true for other patients with primary hypoparathyroidism associated with pernicious anaemia presented in the literature, as well as for the present patient All these patients had symptoms of hypoparathyroidism already in childhood, and it thus seems probable that the disease is at least of congenital origin

It is possible, on the other hand, that hypoparathyroidism was the primary disease and led to cessation of intrinsic factor secretion and, by this route, to pernicious anaemia In the patients of Walsh (12), Wilkins (13), Hurwitz (4) and Reisner and Ellsworth (9), as well as in the present case the signs of hypoparathyroidism preceded by several years the occurrence of megaloblastic anaemia According to Donegan and Spiro (1), a certain level of serum calcium is necessary for adequate function of the gastric mucosa Of the four patients in the present series with inadequately treated post-operative hypoparathyroidism, all had severe superficial gastritis, and one had achlorhydria which disappeared after treatment The superficial gastritis did not respond to treatment of the hypocalcaemia However, our previous (5, 10, 11) studies suggest that the healing of superficial gastritis is not common In contrast, superficial gastritis, once established, tends to persist or progress into atrophic gastritis Hence, it is not impossible that gastritis may be due to hypoparathyroidism and can occasionally lead to deficiency of intrinsic factor

In addition, the manifestation of this deficiency might be accelerated by the deficient absorption of vitamin B_1 due to pathological calcium metabolism (2, 3) On the other hand, it should be noted that the role of gastritis might simply be the manifestation of a pre existing relative intrinsic factor deficiency of hereditary origin This seems plausible from the opinions presented recently by Witts (14)

Summary

One patient suffering from primary hypoparathyroidism associated with Addisonian pernicious anaemia is described In addition, four patients with poorly treated post-operative hypoparathyroidism were studied in order to establish the response of the gastric mucosa to deficient function of the hypoparathyroids All four patients had severe superficial gastritis, and one achlorhydria which disappeared after treatment of the hypocalcaemia In two patients a second gastric biopsy was performed after successful treatment, it revealed persisting superficial gastritis The causal relationship between pernicious anaemia and primary hypoparathyroidism is discussed briefly

Acknowledgement

We wish to express our thanks to B A Lamberg M D for the performance of the calcium balance studies This study was aided by a grant from Sigrid Juselius Foundation

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ciency, pernicious anaemia (in two patients), steatorrhoea and adrenal insufficiency Because the concentrations of sodium and chloride in sweat were increased, they suggested that the syndrome is a variant of mucoviscidosis Although this remained unproved, it seems clear that some genetic defect was involved in these cases This might hold true for other patients with primary hypoparathyroidism associated with pernicious anaemia presented in the literature, as well as for the present patient All these patients had symptoms of hypoparathyroidism already in childhood, and it thus seems probable that the disease is at least of congenital origin

It is possible, on the other hand, that hypoparathyroidism was the primary disease and led to cessation of intrinsic factor secretion and, by this route, to pernicious anaemia In the patients of Walsh (12), Wilkins (13), Hurwitz (4) and Reisner and Ellsworth (9), as well as in the present case the signs of hypoparathyroidism preceded by several years the occurrence of megaloblastic anaemia According to Donegan and Spiro (1), a certain level of serum calcium is necessary for adequate function of the gastric mucosa Of the four patients in the present series with inadequately treated post-operative hypoparathyroidism, all had severe superficial gastritis, and one had achlorhydria which disappeared after treatment The superficial gastritis did not respond to treatment of the hypocalcaemia However, our previous (5, 10, 11) studies suggest that the healing of superficial gastritis is not common In contrast, superficial gastritis, once established, tends to persist or progress into atrophic gastritis Hence, it is not impossible that gastritis may be due to hypoparathyroidism and can occasionally lead to deficiency of intrinsic factor In addition, the manifestation of this deficiency might be accelerated by the deficient absorption of vitamin B_1 due to pathological calcium metabolism (2, 3) On the other hand, it should be noted that the role of gastritis might simply be the manifestation of a pre-existing relative intrinsic factor deficiency of hereditary origin This seems plausible from the opinions presented recently by Witts (14)

Summary

One patient suffering from primary hypoparathyroidism associated with Addisonian pernicious anaemia is described In addition, four patients with poorly treated post operative hypoparathyroidism were studied in order to establish the response of the gastric mucosa to deficient function of the hypoparathyroids All four patients had severe superficial gastritis, and one achlorhydria which disappeared after treatment of the hypocalcaemia In two patients a second gastric biopsy was performed after successful treatment, it revealed persisting superficial gastritis The causal relationship between pernicious anaemia and primary hypoparathyroidism is discussed briefly

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Cytometric Studies of Myeloma Cells

Planimetry and Diameter Measurements in 33 Cases of Myelomatosis with Special Reference to the Correlation Between Cell Size and Serum Immuno-electrophoretic Findings

By

AAGE DRIVSHOLM[1]

In studies involving the use of radioactive isotopes, tissue culture and immuno fluorescence microscopy it has been established within the past few years that the abnormal serum proteins in myelomatosis are formed in the plasma cells (6).

Numerous attempts have been made to correlate the types of myeloma proteins with the morphology of myeloma cells, but the results have varied (6, 18). The immuno-electrophoretic technique has now made it possible to divide the myeloma proteins into three well defined groups γ_{ss}, γ_{1-A} (β_{2A}) and γ_{μ} (Bence Jones protein) (5, 11). Various investigations using this classification have indicated a certain correlation between the occurrence of γ_{1-A} paraprotein in the serum and the presence in bone marrow of plasma cells having one of the following characteristics: 1) Intranuclear inclusion bodies, 2) flamed cytoplasm, 3) thesaurocyte formation (18). However, these relationships need further elucidation (6).

As emphasized in several studies on the cytology of the myeloma cell (1, 3, 8, 14, 17, 19, 20, 21, 23, and 25) the individual myeloma cells vary in atypia, polymorphism and degree of maturity as well as in size of the cells and nuclei. These variations may be observed from one patient to another, but may also occur within the individual bone marrow specimen.

Several studies have been performed on the variation in cell size and nuclear size of myeloma cells in an effort to correlate these parameters to the changes in serum protein (4, 9, 10, 12, 15, 16, 22, 24, and 25). Correlation of cytometric cell size to the types of paraprotein has been reported by Paraskevas et al (18). These authors found that the average size of the myeloma cells in patients with γ_{1-A} paraproteinaemia is significantly larger than that in patients with paraproteinaemia of the γ_{ss} and γ_{μ} (Bence Jones protein) types.

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Table I Planimetry and diameter measurements in 33 patients with myelomatosis $\overline{C}_A$ and $\overline{N}_A$ represent the mean cellular and nuclear area of 50 myeloma cells $\overline{C}$ and $\overline{N}$ refer to the corresponding parameters in the diameter measuring method The terms $C = \frac{L+B}{2}$ and $\lambda = \frac{l+b}{2}$ (cf fig 1) are used to express the cell size of the individual myeloma cells and nuclei in the diameter measurements

Case no	Myeloma cell (%)	Planimetric measurements (μ)							Diameter measurements (μ)							Type of para protein
		$\overline{C}_A$	SD	Coeff of variation	$\overline{N}_A$	SD	Coeff of variation	$\overline{N}_A/\overline{C}_A$	$\overline{C}$	SD	Coeff of variation	$\overline{N}$	SD	Coeff of variation	$\overline{N}/\overline{C}$	
1	35.5	289.0	93.1	33.9	83.5	26.3	31.5	0.29	19.3	3.5	18.3	9.8	1.4	14.7	0.51	γ1-A
2	15.9	250.4	76.5	30.6	92.7	26.1	28.2	0.37	18.2	3.4	18.6	10.5	0.9	8.5	0.58	γss
3	24.3	169.6	62.0	36.6	58.9	15.9	27.0	0.35	14.6	2.5	17.4	8.2	1.3	15.2	0.56	γss
4	94.7	162.0	31.1	19.2	79.1	16.1	20.4	0.49	14.2	1.5	10.2	9.9	1.0	10.4	0.69	γss
5	7.0	147.4	39.4	26.7	63.1	15.7	24.9	0.43	13.9	2.2	16.0	8.4	1.2	14.3	0.61	γss
6	34.9	189.6	72.8	38.4	77.4	20.2	26.1	0.41	15.5	2.8	17.8	9.6	1.9	20.1	0.62	γss
7	16.7	181.2	51.5	28.4	72.7	15.9	21.9	0.40	14.7	3.7	25.4	8.9	0.9	10.6	0.61	γss
8	9.8	215.0	88.3	41.1	73.6	26.[illegible]	35.6	0.34	16.4	3.5	21.1	9.0	1.6	17.8	0.55	γss + γμ
9	15.9	184.5	57.7	31.3	76.0	18.5	24.3	0.41	15.1	2.8	18.7	9.0	1.3	14.6	0.60	γss + γμ
10	41.8	171.9	41.9	24.4	67.2	15.1	22.5	0.39	14.5	1.9	13.3	8.6	1.2	13.7	0.59	γss
11	36.5	145.3	40.3	27.7	72.2	15.7	21.7	0.50	13.3	2.0	14.8	8.9	0.9	10.6	0.67	γss + γμ
12	60.2	372.5	106.3	28.5	131.5	14.4	11.0	0.35	21.4	3.3	15.6	[illegible]	1.1	18.6	0.57	γ1-A
13	16.5	262.2	94.3	36.0	111.9	42.7	38.2	0.43	17.7	2.8	15.7	11.1	2.0	15.7	0.62	γμ
14	35.7	278.3	96.5	34.7	93.8	26.6	28.4	0.34	18.6	3.3	17.7	9.9	2.0	20.4	0.53	γ1-A
15	36.6	184.3	58.1	31.5	72.3	18.7	25.9	0.39	14.6	2.2	14.9	8.7	1.2	13.3	0.59	γss
16	55.3	285.2	74.3	26.1	97.3	22.4	23.0	0.34	18.4	2.4	12.9	10.4	1.5	14.3	0.56	γss
17	34.0	248.9	81.0	32.5	95.8	29.0	30.3	0.39	17.0	2.5	14.8	9.8	1.7	16.9	0.58	γss + γμ
18	18.0	222.6	54.9	24.7	78.8	16.7	21.2	0.35	16.1	2.1	12.6	9.0	1.1	12.1	0.56	γss
19	43.0	183.2	40.4	22.1	77.0	14.7	19.1	0.42	14.7	1.8	12.5	8.8	1.0	11.5	0.60	γμ
20	91.0	137.1	27.5	20.1	69.9	11.9	17.0	0.51	12.5	1.6	12.5	8.4	0.8	9.6	0.67	γss
21	34.6	221.6	84.3	38.0	82.3	27.1	32.9	0.37	16.2	3.2	20.0	9.3	1.8	18.8	0.57	γ1-A
22	35.8	178.6	65.5	36.7	84.6	23.9	28.3	0.47	14.4	2.8	19.3	9.5	1.5	15.5	0.66	γss
23	54.2	312.7	104.9	33.5	103.0	27.0	26.2	0.33	19.7	3.6	18.2	10.8	1.7	15.8	0.55	γ1-A
24	11.9	206.1	61.6	29.9	78.4	22.4	28.6	0.38	15.6	2.3	14.5	9.0	1.4	15.4	0.59	γ1-A
25	27.4	217.3	70.8	32.6	92.2	26.1	28.3	0.42	15.8	2.6	16.6	9.8	1.6	16.6	0.62	γss
26	24.4	218.3	61.4	28.1	83.6	17.1	20.5	0.38	10.9	2.2	14.0	9.2	1.8	19.1	0.58	γss
27	42.8	240.8	90.0	37.4	102.8	25.1	24.4	0.43	16.6	3.0	18.3	10.0	1.4	14.3	0.60	γss
28	26.4	311.5	90.1	28.9	96.6	11.1	11.5	0.31	19.0	3.2	16.8	10.1	0.7	7.1	0.53	γss
29	72.5	189.2	69.4	36.7	72.1	10.9	15.1	0.38	14.5	2.6	17.7	8.6	1.2	14.0	0.59	γss + γμ
30	22.5	249.5	46.6	18.7	126.9	14.3	11.3	0.51	17.1	1.5	8.8	11.2	0.7	6.1	0.66	γ1-A
31	42.6	182.6	38.9	21.3	67.2	47.3	17.5	0.37	14.8	1.8	12.1	8.2	0.7	8.6	0.55	γμ
32	42.4	236.2	94.1	39.8	79.2	27.0	34.1	0.34	16.5	4.0	24.4	9.1	2.1	22.6	0.55	γ1-A
33	75.5	204.7	49.4	24.1	97.1	20.1	20.7	0.47	15.3	1.8	11.9	10.0	1.1	11.0	0.65	γss

areas were calculated Ten measurements were done on each cell giving a coefficient of variation of less than 3% The mean of 10 measurements on the cell was called C_A the mean of planimetry on 50 cells $\overline{C}_A$

Corresponding measurements were made on the cell nuclei $\frac{l+b}{2}$ was designated as N (cf fig 1) and the mean of 10 planimetric measurements on one nucleus N_A The cor

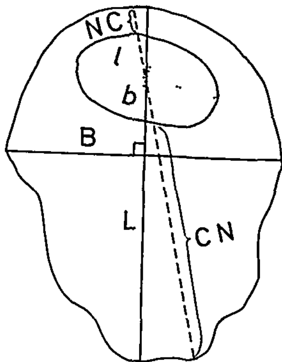


Fig 1 Model of myeloma cell showing the parameters used in the diameter measurements L is the maximum longitudinal diameter of the cell B the maximum transverse diameter at right angles on L l and b are the corresponding nuclear measurements C $\left(=\frac{L+B}{2}\right)$ is used as a measure of cell size N $\left(=\frac{l+b}{2}\right)$ as a measure of nuclear size The designations NC and CN signify the minimum and maximum distances from the nuclear to the cellular margin $\frac{NC}{CN}$ is used as a relative measure of the eccentricity of the nucleus called E (eccentricity index)

considered together Moreover, the "γ_{1-A} myeloma cells" had a smaller nuclear/cell ratio than the cells in myelomatosis of the $\gamma_{ss} + \gamma_{\mu}$ type The present study of planimetric and diameter measurements on bone marrow specimens from 33 patients with myelomatosis was undertaken to elucidate 1) The variation in the size of the myeloma cells in the individual patients, 2) the variations in the size of the myeloma cells from one patient to another, 3) the correlation between the average size of the myeloma cells in the individual patient and the type of the paraprotein component in the serum, and 4) the correlations between diameter measurements and planimetry

Material

The investigation comprises 33 consecutive patients from a series of 105 cases of myelomatosis (7) The diagnosis of myelomatosis was based primarily on bone marrow examinations and was later confirmed by immuno-electrophoretic studies All cytological studies were performed before the immuno-electrophoretic findings were known

Methods

The cellular measurements were done by projecting the cells, in a magnification of 1000 x, onto a piece of Whatman paper No 0, *stretched on a glass plate on the table in front* of the investigator The projection was made by a microscope suspended with the optical axis horizontally and a prism inserted instead of the ocular The illumination was by a mercury super pressure lamp (Osram H B 0 200 W)

Prior to the measurement of the cells in each individual preparation the degree of magnification was checked by replacing the specimen by an object micrometer (C Zeiss, Germany) The measurements were carried out close to the centre of the field to secure geometry from one preparation to the other the margin of the cell or the nucleus being projected onto a fixed point on the paper

Diameter measurements An adjusted ruler was used The maximum cell diameter, designated L, and the maximum diameter at right angles to L, designated B were measured $\frac{L+B}{2}$ was used as a value of the cell size and designated C The average of the 50 cell measurements was designated $\overline{C}$

Planimetry was done by a planimeter (K Murbach Switzerland), adjusted for absolute measurements by preliminary studies of cells of circular or ellipsoid shape in which the

Table I Planimetry and diameter measurements in 33 patients with myelomatosis $\bar{C}_A$ and $\bar{N}_A$ represent the mean cellular and nuclear area of 50 myeloma cells $\bar{C}$ and $\bar{N}$ refer to the corresponding parameters in the diameter measuring method The terms $C = \frac{L+B}{2}$ and $N = \frac{l+b}{2}$ (cf fig 1) are used to express the cell size of the individual myeloma cells and nuclei in the diameter measurements

Case no	Myeloma cell (%)	Planimetric measurements (μ^2)							Diameter measurements (μ)							Type of para protein
		$\bar{C}_A$	SD	Coeff of variation	$\bar{N}_A$	SD	Coeff of variation	$\bar{N}_A/\bar{C}_A$	$\bar{C}$	SD	Coeff of variation	$\bar{N}$	SD	Coeff of variation	$\bar{N}/\bar{C}$	
1	35.5	289.0	98.1	33.9	83.5	26.3	31.5	0.29	19.3	3.5	18.3	9.8	1.4	14.7	0.51	γL-λ
2	15.9	250.4	76.5	30.6	92.7	26.1	28.2	0.37	18.2	3.4	18.6	10.5	0.9	8.5	0.58	γss
3	24.3	169.6	62.0	36.6	58.9	15.9	27.0	0.35	14.6	2.5	17.4	8.2	1.3	15.2	0.56	γss
4	94.7	162.0	31.1	19.2	79.1	16.1	20.4	0.49	14.2	1.5	10.2	9.9	1.0	10.4	0.69	γss
5	7.0	147.4	39.4	26.7	63.1	15.7	24.9	0.43	13.9	2.2	16.0	8.4	1.2	14.3	0.61	γss
6	34.0	189.6	72.8	38.4	77.4	20.2	26.1	0.41	15.5	2.8	17.8	9.6	1.9	20.1	0.62	γss
7	16.7	181.2	51.5	28.4	72.7	15.9	21.9	0.40	14.7	3.7	25.4	8.9	0.9	10.6	0.61	γss
8	9.8	215.0	88.3	41.1	73.6	26.2	35.6	0.34	16.4	3.5	21.1	9.0	1.6	17.8	0.55	γss + γμ
9	15.9	184.5	57.7	31.3	76.0	18.5	24.3	0.41	15.1	2.8	18.7	9.0	1.3	14.6	0.60	γss + γμ
10	41.8	171.3	41.9	24.4	67.2	15.1	22.5	0.39	14.[illegible]	1.9	13.3	8.6	1.2	13.7	0.59	γss
11	26.5	145.3	40.3	27.7	72.2	15.7	21.7	0.50	13.3	2.0	14.8	8.9	0.9	10.5	0.67	γss + γμ
12	60.2	372.[illegible]	106.3	28.5	131.5	14.4	11.0	0.35	21.4	3.3	15.6	12.1	1.1	18.6	0.57	γL-λ
13	16.5	262.2	91.3	36.0	111.9	42.7	38.2	0.43	17.7	2.8	15.7	11.1	2.0	15.7	0.62	γμ
14	25.7	278.3	96.5	34.7	93.8	26.6	28.4	0.34	18.6	3.3	17.7	9.9	2.0	20.4	0.53	γL-λ
15	36.6	184.3	58.1	31.5	72.3	18.7	25.9	0.39	14.6	2.2	14.9	8.7	1.2	13.3	0.59	γss
16	[illegible]5.3	285.2	74.3	26.1	97.3	22.4	23.0	0.34	18.4	2.4	17.9	10.4	1.6	14.3	0.56	γss
17	34.0	248.9	81.0	32.5	95.8	29.0	30.3	0.39	17.0	2.5	14.8	9.8	1.7	16.9	0.58	γss + γμ
18	18.0	272.6	54.9	24.7	78.8	16.7	21.4	0.3[illegible]	16.1	2.1	12.6	9.0	1.1	12.1	0.56	γss
19	43.0	183.2	40.4	22.1	77.0	14.7	19.1	0.42	14.7	1.8	12.5	8.8	1.0	11.5	0.60	γμ
20	91.0	137.1	27.5	20.1	69.9	11.9	17.0	0.51	12.5	1.6	12.5	8.4	0.8	9.6	0.67	γss
21	34.6	221.6	84.3	38.0	82.3	27.1	32.9	0.37	16.2	3.2	20.0	9.3	1.8	18.8	0.57	γL-λ
22	35.8	178.6	65.5	36.7	84.6	23.9	28.3	0.47	14.4	2.8	19.3	9.5	1.5	15.5	0.66	γss
23	54.2	312.7	104.9	33.5	103.0	27.0	26.2	0.33	19.7	3.6	18.2	10.8	1.7	15.8	0.55	γL-λ
24	11.9	205.1	61.6	29.9	78.4	22.4	28.6	0.38	15.6	2.3	14.5	9.0	1.4	15.4	0.59	γL-λ
25	22.4	217.3	70.8	32.6	92.2	26.1	28.3	0.42	15.8	2.6	16.6	9.8	1.6	16.6	0.62	γss
26	24.4	218.3	61.4	28.1	83.6	17.1	20.5	0.39	10.9	2.2	14.0	9.2	1.8	19.1	0.58	γss
27	42.8	240.8	90.0	37.4	102.8	25.1	24.4	0.43	16.6	3.0	18.3	10.0	1.4	14.3	0.60	γss
28	26.4	311.5	90.1	28.9	96.6	11.1	11.5	0.31	19.0	3.2	16.8	10.1	0.7	7.1	0.53	γss
29	22.5	189.2	69.4	36.7	72.1	10.9	15.1	0.38	14.5	2.6	17.7	8.6	1.2	14.0	0.59	γss + γμ
30	27.5	249.5	46.6	18.7	126.9	14.3	11.3	0.51	17.1	1.5	8.8	11.2	0.7	6.1	0.66	γL-λ
31	42.6	182.6	38.9	21.3	67.2	[illegible]	17.5	0.37	14.8	1.8	12.1	8.2	0.7	8.6	0.55	γμ
32	42.4	236.0	94.1	[illegible]8	79.2	27.0	34.1	0.34	16.5	4.0	24.4	9.1	2.1	22.6	0.55	γL-λ
33	75.5	204.7	49.4	24.1	97.1	20.1	20.7	0.47	15.3	1.8	11.9	10.0	1.1	11.0	0.65	γss

areas were calculated Ten measurements were done on each cell giving a coefficient of variation of less than 3% The mean of 10 measurements on the cell was called C_A the mean of planimetry on 50 cells $\bar{C}_A$

Corresponding measurements were made on the cell nuclei $\frac{l+b}{2}$ was designated as N (cf fig 1) and the mean of 10 planimetric measurements on one nucleus N_A The cor

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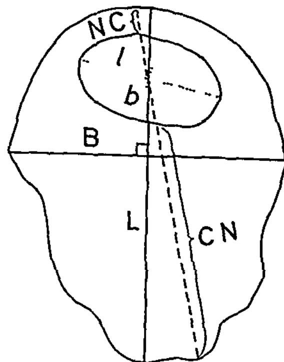


Fig 1 Model of myeloma cell showing the parameters used in the diameter measurements L is the maximum longitudinal diameter of the cell B the maximum transverse diameter at right angles on L l and b are the corresponding nuclear measurements C $\left(= \frac{L + B}{2}\right)$ is used as a measure of cell size, N $\left(= \frac{l + b}{2}\right)$ as a measure of nuclear size The designations NC and CN signify the minimum and maximum distances from the nuclear to the cellular margin $\frac{NC}{CN}$ is used as a relative measure of the eccentricity of the nucleus called E (eccentricity index)

considered together Moreover, the "γ_{1-A} myeloma cells" had a smaller nuclear/cell ratio than the cells in myelomatosis of the $\gamma_{ss} + \gamma_{\mu}$ type The present study of planimetric and diameter measurements on bone-marrow specimens from 33 patients with myelomatosis was undertaken to elucidate 1) The variation in the size of the myeloma cells in the individual patients, 2) the variations in the size of the myeloma cells from one patient to another, 3) the correlation between the average size of the myeloma cells in the individual patient and the type of the paraprotein component in the serum, and 4) the correlations between diameter measurements and planimetry

Material

The investigation comprises 33 consecutive patients from a series of 105 cases of myelomatosis (7) The diagnosis of myelomatosis was based primarily on bone-marrow examinations and was later confirmed by immunoelectrophoretic studies All cytological studies were performed before the immuno-electrophoretic findings were known

Methods

The cellular measurements were done by projecting the cells, in a magnification of 1000 ×, onto a piece of Whatman paper No 0, stretched on a glass plate on the table in front of the investigator The projection was made by a microscope suspended with the optical axis horizontally and a prism inserted instead of the ocular The illumination was by a mercury super-pressure lamp (Osram H B 0 200 W)

Prior to the measurement of the cells in each individual preparation the degree of magnification was checked by replacing the specimen by an object micrometer (C Zeiss, Germany) The measurements were carried out close to the centre of the field to secure geometry from one preparation to the other the margin of the cell or the nucleus being projected onto a fixed point on the paper

Diameter measurements An adjusted ruler was used The maximum cell diameter, designated L and the maximum diameter at right angles to L designated B, were measured $\frac{L + B}{2}$ was used as a value of the cell size and designated C The average of the 50 cell measurements was designated $\bar{C}$

Planimetry was done by a planimeter (K Murbach, Switzerland), adjusted for absolute measurements by preliminary studies of cells of circular or ellipsoid shape in which the

Table I *Planimetry and diameter measurements in 33 patients with myelomatosis* $\bar{C}_A$ *and* $\bar{N}_A$ *represent the mean cellular and nuclear area of 50 myeloma cells* $\bar{C}$ *and* $\bar{N}$ *refer to the corresponding parameters in the diameter measuring method The terms* $C = \frac{L+B}{2}$ *and* $N = \frac{l+b}{2}$ *(cf fig 1) are used to express the cell size of the individual myeloma cells and nuclei in the diameter measurements*

Case no	Myeloma cell (%)	Planimetric measurements (μ^2) $\bar{C}_A$	SD	Coeff of variation	$\bar{N}_A$	SD	Coeff of variation	$\bar{N}_A/\bar{C}_A$	Diameter measurements (μ) $\bar{C}$	SD	Coeff of variation	$\bar{N}$	SD	Coeff of variation	$\bar{N}/\bar{C}$	Type of para protein
1	35.5	289.0	98.1	33.9	83.5	26.3	31.5	0.29	19.3	3.5	18.3	9.8	1.4	14.7	0.51	γI-A
2	15.9	250.4	76.5	30.6	92.7	26.1	28.2	0.37	18.2	3.4	18.6	10.5	0.9	8.5	0.58	ss
3	24.3	169.6	62.0	36.6	59.9	15.9	27.0	0.35	14.6	2.5	17.4	8.2	1.3	15.2	0.56	γss
4	94.7	162.0	31.1	19.2	79.1	16.1	20.4	0.49	14.2	1.5	10.2	9.9	1.0	10.4	0.69	γss
5	7.0	147.4	39.4	26.7	63.1	15.7	24.9	0.43	13.9	2.2	16.0	8.4	1.2	14.3	0.61	γss
6	34.9	189.6	72.8	38.4	77.4	20.2	26.1	0.41	15.5	2.8	17.8	9.6	1.9	20.1	0.62	γss
7	16.7	181.2	51.5	28.4	72.7	15.9	21.9	0.40	14.7	3.7	25.4	8.9	0.9	10.6	0.61	γss
8	9.8	215.0	88.3	41.1	73.6	26.2	35.6	0.34	16.4	3.5	21.1	9.0	1.6	17.8	0.55	γss + γμ
9	15.9	184.[illegible]	57.7	31.3	76.0	18.5	24.3	0.41	15.1	2.8	18.7	9.0	1.3	14.6	0.60	γss + γL
10	41.8	171.9	41.9	24.4	67.2	15.1	22.5	0.39	14.5	1.9	13.3	8.6	1.2	13.7	0.59	γss
11	36.5	145.3	40.3	27.7	72.2	15.7	21.7	0.50	13.3	2.0	14.8	8.9	0.9	10.6	0.67	γss + γμ
12	60.2	372.5	106.3	28.5	131.5	14.4	11.0	0.35	21.4	3.3	15.6	12.1	1.1	18.6	0.57	γI-A
13	16.5	262.2	91.3	36.0	111.9	42.7	38.2	0.43	17.7	2.8	15.7	11.1	2.0	15.7	0.62	γμ
14	35.7	278.3	96.5	34.7	93.8	26.6	28.4	0.34	18.6	3.3	17.7	9.9	2.0	20.4	0.53	γI-A
15	26.6	184.3	58.1	31.5	77.3	18.7	25.9	0.39	14.6	2.2	14.9	8.7	1.2	13.3	0.59	γss
16	35.3	285.2	74.3	26.1	97.3	22.4	23.0	0.34	18.4	2.4	12.9	10.4	1.5	14.3	0.56	γss
17	34.0	248.9	81.0	32.5	95.8	29.0	30.3	0.39	17.0	2.5	14.8	9.8	1.7	16.9	0.58	γss + [illegible]
18	18.0	222.6	54.9	24.7	78.8	16.7	21.2	0.35	16.1	2.1	12.6	9.0	1.1	12.1	0.56	γss
19	43.0	183.2	40.4	22.1	77.0	14.7	19.1	0.47	14.7	1.8	12.5	8.8	1.0	11.5	0.60	γμ
20	91.0	137.1	27.5	20.1	69.9	11.9	17.0	0.51	12.5	1.6	12.5	8.4	0.8	9.6	0.67	γss
21	34.6	221.6	84.3	38.0	82.3	27.1	32.9	0.37	16.2	3.2	20.0	9.3	1.8	18.8	0.57	γI-A
22	35.8	178.6	65.5	36.7	84.6	23.9	28.3	0.47	14.4	2.8	19.3	9.5	1.5	15.5	0.66	γss
23	54.2	312.7	104.9	33.5	103.0	27.0	26.2	0.33	19.7	3.6	18.2	10.8	1.7	15.8	0.55	γI-A
24	11.9	206.1	61.6	29.9	78.4	22.4	28.6	0.38	15.6	2.3	14.5	9.0	1.4	15.4	0.58	γI-A
25	22.4	217.3	70.8	32.6	92.2	26.1	28.3	0.42	15.8	2.6	16.6	9.8	1.6	16.6	0.62	γss
26	24.4	218.3	61.4	28.1	83.6	17.1	20.5	0.38	10.9	2.2	14.0	9.2	1.8	19.1	0.58	γss
27	42.8	240.8	90.0	37.4	102.8	25.1	24.4	0.43	16.6	3.0	18.3	10.0	1.4	14.3	0.60	γss
28	26.4	311.5	90.1	28.9	96.6	11.1	11.5	0.31	19.0	3.2	16.8	10.1	0.7	7.1	0.53	γss
29	22.5	189.2	69.4	36.7	72.1	10.9	15.1	0.38	14.5	2.6	17.7	8.6	1.2	14.0	0.59	γss + γμ
30	22.5	249.5	46.6	18.7	126.9	14.3	11.3	0.51	[illegible]	1.5	8.8	11.2	0.7	6.1	0.66	γI-A
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33	75.5	204.7	19.4	24.1	97.1	20.1	20.7	0.47	15.3	1.8	11.9	10.0	1.1	11.0	0.65	γss

areas were calculated Ten measurements were done on each cell giving a coefficient of variation of less than 3% The mean of 10 measurements on the cell was called C_A the mean of planimetry on 50 cells $\bar{C}_A$

Corresponding measurements were made on the cell nuclei $\frac{l+b}{2}$ was designated as N (cf fig 1) and the mean of 10 planimetric measurements on one nucleus N_A The cor

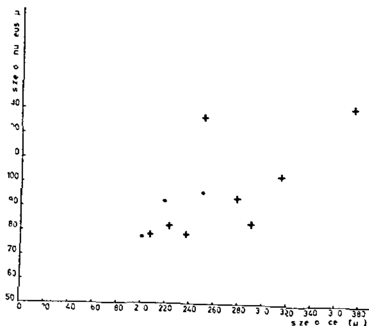


Fig 2 Planimetry of myeloma cells in 33 patients the mean nuclear/cell ratio being given for the individual patients + indicates patients having γ1 A paraproteinaemia · patients having paraproteinaemia of the γss and μ type

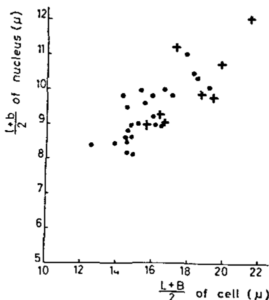


Fig 3 Diameter measurements of myeloma cells in 33 patients the mean nuclear/cell ratio being given for in the individual patients + and · indicate γ1 A paraproteinaemia and paraproteinaemia of the γss and γμ types respectively

responding means of measurements on 50 nuclei were designated as $\overline{N}$ and $\overline{N}_A$ respectively

In order to evaluate the position of the nucleus in each individual cell (cf fig 1) measurements were made on a line through the centre of the nucleus to the point on the periphery of the cell having the shortest distance from the margin of the nucleus The longer distance from cell to nuclear margin was called CN the shorter NC (cf fig 1) $\frac{NC}{CN}$ was used as a measure of the position of the nucleus in the individual myeloma cells and designated E (index of eccentricity) The mean value of E in measurements of 50 myeloma cells in each preparation was called $\overline{E}$

In order to describe the individual myeloma cell the colour of the cytoplasm (bluish greyish blue grey) the cytoplasmic outlines (regular irregular notched) the presence of archoplasm (± Hof) and vacuoles in the cytoplasm (± V) were recorded For the nucleus the content of nucleoli (+ nucl) and possible inclusion bodies were noted

The measurements of the cells were done in all cases on May Grunwald Giemsa stained smears of bone marrow Fifty myeloma cells of each preparation were submitted to simultaneous measurements of the diameter and planimetric parameters of cell and nucleus The bone marrow preparations were smeared undiluted and without the use of anticoagulants As far as possible preparations from the first diagnostic puncture were used The term myeloma cells as used in this paper includes plasma cells and plasmocytic reticulum cells as it was felt that a distinction between normal and pathological plasma cells in the bone marrow of a patient with myelomatosis can

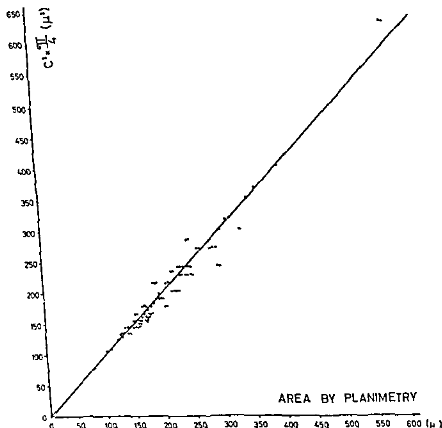


Fig 4 Correlation between area measured by planimetry and area calculated from diameter measurements Values from 200 individual cells. The correlation coefficient (r) is 0 96

not be achieved in all cases The term "plasmocytic reticulum cells" is used for reticulum cells with a plasmocytoid appearance i. e with a more basophilic cytoplasm and a more condensed chromatin than normally seen in reticulum cells The distinction between plasmocytic reticulum cells and ordinary reticulum cells is difficult and mainly a matter of subjective evaluation The same applies to the differentiation between immature plasma cells and plasmocytic reticulum cells. Measurements were done on all myeloma cells in a given field provided that the cells showed a distinct demarcation of the cytoplasm The investigations of the cells were done in sites where the individual cells containing nuclei did not touch but never quite at the margin of the preparations where the cells often show peripheral fraying No measurements were done on myeloma cells containing more than one nucleus

Results

Table I gives the values for diameter and planimetric parameters The per cent number of myeloma cells was obtained by counting 1,000 cells containing nuclei in each preparation The last column gives the paraprotein components in the patients concerned The number of patients having γ_{1-A} paraproteinaemia (8 of 33) corresponds approximately to the distri-

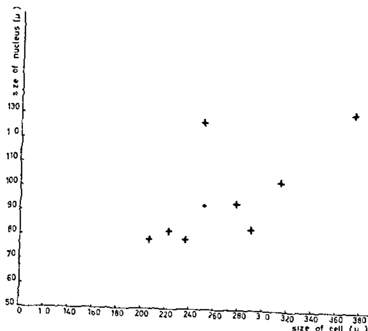


Fig 2 Planimetry of myeloma cells in 33 patients the mean nuclear/cell ratio being given for the individual patients + indicates patients having γ_{1-A} paraproteinaemia pa tients having paraproteinaemia of the γ_{SS} and γ_{μ} type

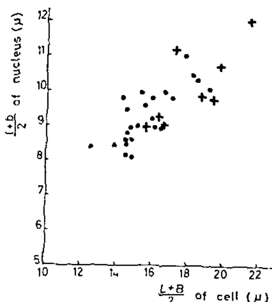


Fig 3 Diameter measurements of *myeloma cells* in 33 patients the mean nuclear/cell ratio being given for in the individual patients + and indi cate γ_{1-A} paraproteinaemia and *paraproteinaemia* of the γ_{SS} and γ_{μ} types respectively

responding means of measurements on 50 nu clei were designated as $\bar{N}$ and $\bar{N}_A$ respectively

In order to evaluate the position of the nucleus in each individual cell (cf fig 1), measurements were made on a line through the centre of the nucleus to the point on the periphery of the cell having the shortest distance from the margin of the nucleus The longer distance from cell to nuclear margin was called CN the shorter NC (cf fig 1) $\frac{NC}{CN}$ was used as a measure of the position of the nucleus in the individual myeloma cells and designated L (index of eccentricity) The mean value of I in measurements of 50 myeloma cells in each preparation was called $\bar{E}$

In order to describe the individual myeloma cell, the colour of the cytoplasm (bluish greyish blue, grey), the cytoplasmic outlines (regular irregular, notched), the presence of archoplasm (± Hof), and vacuoles in the cy*toplasm* (*± V*) *were recorded For the nu* cleus, the content of nucleoli (± nucl) and possible inclusion bodies were noted

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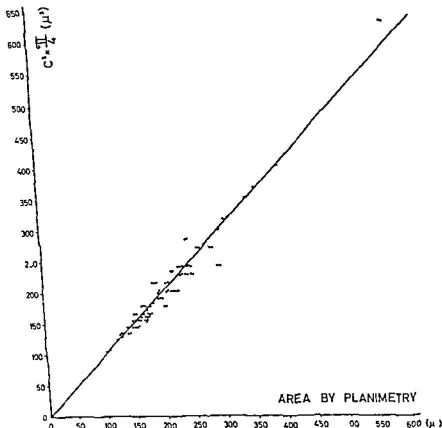


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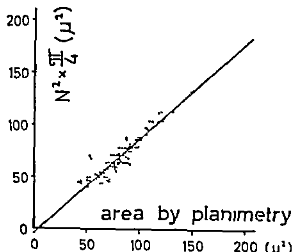


Fig 5 Correlation between area measured by planimetry and area calculated *from diameter* measurements Values from 200 individual nuclei The correlation coefficient (r) is 0 95

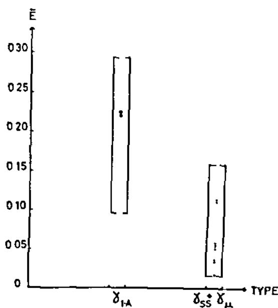


Fig 6 Correlation between mean eccentricity index $\left(\bar{E} = \frac{NC}{CN} \text{ cf fig 1}\right)$ and type of paraproteinaemia in 33 patients with myelomatosis

bution in a material of 105 cases of myelomatosis published previously (6)

As may be seen from the standard deviations and the corresponding coefficients of variation (13) in table I, the cells within the majority of preparations showed mark ed *variations in size* The nuclear size also varied widely, although the individual variation is less for the nuclei than for the cells In a few preparations, however, only minor variations in cell and nuclear size were seen (for example cases 20, 30, and 31)

The mean size of the cells and nuclei ($\bar{C}_V$, $\bar{C}$, $\bar{N}_V$, and $\bar{N}$) also varies widely *from one preparation to the other* The average nuclear/cell ratio in the individual patients may be read from table I but is more clearly apparent from figs 2 and 3 in which the nuclear/cell ratio is plotted from the planimetric and diameter measurements respectively

The mean size of 50 myeloma cells and their nuclei in one smear is related in table I to the type of paraprotein in the patient's serum The mean cell size in patients having γ_{1-A} *paraproteinaemia is greater than* that in patients with other types of paraproteinaemia (γ_{ss} and γ_{μ} *(Bence-Jones* protein)), although there is a marked overlapping between the two groups (cf figs 2 and 3) As may be seen in table III, this difference is significant in regard to both planimetry and diameter measurements In contrast, there is no significant difference in nuclear size or in nuclear/cell ratio between patients having γ_{1-A} paraproteinaemia on the one hand and patients having γ_{ss} and γ_{μ} paraproteinaemia on the other

A comparison between the area obtain ed by planimetry and the area calculated on the basis of diameter measurements *shows that the results are closely correlat*ed (figs 4 and 5) The diameter, as measured *in the present study, thus gives a* valid relative figure for the size of the cell

The result of the measurements of nu clear eccentricity within the individual preparations is shown in table II which

Table II Measurements of nuclear eccentricity and morphological data of 50 myeloma cells in 33 patients E indicates the eccentricity index $\left(\frac{NC}{CN}\right.$ cf fig $\left.1\right)$ and $\overline{E}$ the mean value for 50 myeloma cells

Case no	Myeloma cell (%)	Per cent myeloma cells with					Eccentr of nucleus		Type of para protein
		Nucleoli	Hof	Greyish cyto plasm	Vacuoles in cyto-plasm	Regular cell outline	$\overline{E}$	SD	
1	35.5	40	–	40	8	48	0.26	0.26	γ_{1-A}
2	15.9	44	–	46	14	36	0.15	0.18	γss
3	24.3	36	–	48	8	94	0.06	0.09	γss
4	94.7	62	–	80	2	86	0.08	0.14	γss
5	7.9	12	54	24	6	72	0.09	0.09	γss
6	34.9	36	70	24	6	68	0.11	0.12	γss
7	16.7	20	90	44	14	74	0.09	0.15	γss
8	9.8	38	88	16	10	28	0.11	0.16	$\gamma ss+\gamma_\mu$
9	15.9	44	90	40	16	48	0.07	0.10	$\gamma ss+\gamma_\mu$
10	41.8	16	96	32	14	68	0.03	0.07	γss
11	36.5	26	94	8	0	88	0.05	0.13	$\gamma ss+\gamma_\mu$
12	60.2	70	52	50	24	60	0.29	0.25	γ_{1-A}
13	16.5	66	84	22	10	52	0.05	0.08	γ_μ
14	35.7	66	90	42	2	56	0.13	0.15	γ_{1-A}
15	36.6	38	94	32	2	54	0.14	0.16	γss
16	55.3	72	90	18	6	54	0.08	0.12	γss
17	34.0	52	98	28	4	56	0.04	0.12	$\gamma ss+\gamma_\mu$
18	18.0	50	98	12	0	76	0.16	0.18	γss
19	43.0	38	94	4	2	76	0.06	0.12	γ_μ
20	91.0	54	98	46	88	88	0.06	0.09	γss
21	34.6	32	96	26	0	34	0.10	0.17	γ_{1-A}
22	35.8	32	88	28	4	70	0.05	0.12	γss
23	54.2	62	46	60	6	22	0.23	0.23	γ_{1-A}
24	11.9	44	78	20	18	54	0.22	0.23	γ_{1-A}
25	22.4	38	94	6	24	64	0.05	0.10	γss
26	24.4	40	98	8	12	54	0.06	0.18	γss
27	42.8	42	88	22	30	50	0.08	0.16	γss
28	26.4	42	62	50	24	28	0.12	0.19	γss
29	22.5	26	86	34	12	72	0.07	0.16	$\gamma ss+\gamma_\mu$
30	22.5	40	50	78	8	36	0.15	0.20	γ_{1-A}
31	42.6	40	76	46	6	32	0.16	0.20	γss
32	42.4	16	78	40	4	42	0.10	0.15	γ_{1-A}
33	75.5	72	84	12	0	70	0.02	0.02	γss

lists the $\overline{E}$ values (eccentricity index) Here too there is a significant difference between the γ_{1-A} group and the group with γss and γ_μ paraproteinaemia (table III), the myeloma cells in the latter group having on an average a more eccentrically placed nucleus (a lower eccentricity index) than the corresponding cells in the γ_{1-A} group The individual $\overline{E}$ values are depicted in fig 6 which also shows the overlapping of the two groups

The number of myeloma cells having (1) nucleoli (2) Hof , (3) greyish cytoplasm, (4) vacuoles in the cytoplasm, and (5) regular cell outlines in the individual patients is given in table II

Table III Mean values for the parameters listed in tables I and II. The $\bar{C}_A$ and $\bar{N}_A$ values are stated in μ^2, C and N in μ. The γ_{1-A} group includes 8 patients, the $\gamma_{ss} + \gamma_\mu$ group 25 patients. The level of significance is $P \leq 0.02$

	Parameter	γ_{1-A} group				$\gamma_{ss} + \gamma_\mu$ group				P value
		Mean value	SD	Coeff of variation	Mean error	Mean value	SD	Coeff of variation	Mean error	
Planimetry	$\bar{C}_A$	270.74	54.44	20.11	19.25	203.34	43.90	21.59	8.78	< 0.01
	$\bar{N}_A$	97.33	21.35	21.74	7.55	81.28	13.58	16.71	2.72	< 0.1
	$\bar{N}_A/\bar{C}_A$	0.36	0.07	19.44	0.02	0.41	0.05	12.20	0.01	< 0.1
Diameter measurements	$\bar{C}$	18.03	2.02	11.20	0.71	15.51	1.62	10.45	0.32	< 0.01
	$\bar{N}$	10.15	1.11	10.94	0.39	9.29	0.78	8.39	0.16	< 0.05
	$\bar{N}/C$	*0.56*	*0.04*	*7.09*	*0.02*	*0.60*	*0.04*	*6.64*	*0.01*	*< 0.05*
Per cent myeloma cells with	Nucleoli	50.0	7.6	15.2	2.7	42.2	16.0	37.9	3.2	> 0.1
	'Hof'	70.0	20.4	29.1	7.2	87.0	11.8	13.6	2.4	< 0.1
	Greyish cytoplasm	44.5	18.5	41.6	6.5	29.2	17.9	61.3	3.6	< 0.05
	Vacuoles in cytoplasm	8.8	8.2	93.2	2.9	12.8	17.5	136.7	3.5	> 0.1
	Regular cell outline	44.0	12.9	29.4	4.6	62.3	18.8	30.1	3.8	< 0.02
	$\bar{E}$	0.18	0.07	38.89	0.03	0.08	0.04	50.00	0.01	< 0.01

On relating the above parameters to the type of the paraproteinaemia, we find the number of myeloma cells with regular outlines to be significantly smaller in the group of γ_{1-A} paraproteinaemia than in the group of γ_{ss} and γ_μ paraproteinaemia (table III) despite a marked overlapping of the two groups. The number of myeloma cells with regular outlines in the individual patients is shown in fig 7. No correlation could be demonstrated between the other parameters and the type of the paraproteinaemia (table III).

Discussion

The value of cellular measurement in smears of bone marrow is often discussed. It is maintained that the smearing injures the cells and that the area of the cells varies with the force used in the smearing (2). Gormsen (8) has studied the variations of plasma-cell size in smears from the bone marrow of 10 normal subjects. With an ocular micrometer he measured in each preparation the maximum longitudinal and transverse diameters of 50 cells and their nuclei. The study revealed that the size of plasma cells — assessed by these parameters — was very constant, with respect both to the cells proper and to the nuclei. This must be interpreted as signifying that the procedure of smearing does not materially affect the relative size relations of *normal* plasma cells.

It is more difficult to assess the findings in abnormal plasma cells such as those present in myelomatosis. The character-

istic features of the myeloma cells are atypia, polymorphism, and varying size of the cells, nuclei, and nuclear/cell ratio The fact that nearly all smears from patients with myelomatosis show myeloma cells with irregular outlines might indicate that at least some factors connected with the smearing gave rise to alterations in their outlines However a number of these patients show forms transitional be tween reticulum cells and normal plasma cells Furthermore, reticulum cells usu ally show irregular outlines in smears Thus, there is no possibility of assessing objectively the share of the technique of smearing the bone marrow in the occur rence of myeloma cells with irregular out lines In studying smears it must be ac cepted that myeloma cells do not mani fest themselves as well defined geometric figures for example as circles or ellip es Therefore, it cannot be expected that the diameter measurements will in all cases afford a real measure of the size of the myeloma cells By planimetry, using the technique described in this paper, it is possible to measure the myeloma cells and their nuclei with a coefficient of variation of less than 3 % Consequently it seems justified to assess on this basis the size of myeloma cells in smears It is of interest also to compare the collected data with the results obtained simultaneously by measurements of the diameters of the cells as in previous studies of myeloma cells (4 8 9 12 16 18 22 24 and 25), in order to assess the value of the latter method

The result of the present diameter measurements corresponds exactly to those found by previous authors using diameter measurements by ocular microm eter (4 8 9 12 16 22 24 25) This means that the myeloma cells in the pres ent study are comparable with those in the previous studies

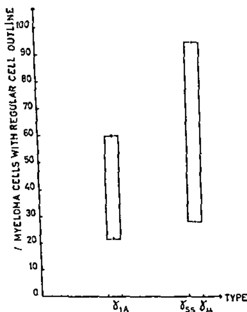


Fig 7 Correlation between per cent of myeloma cells with regular cell outline and type of para protein in 33 patients with myelomatosis

Comparison of the results obtained by planimetry and by diameter measure ments shows that the results are com parable This seems to confirm for the first time the current assumption that meas urements of diameter are sufficient for rel ative measurements even in dealing with cells having irregular outlines such as mye- loma cells

These investigations confirmed the gen eral impression gained by the micro scopic study of smears that the myeloma cells vary widely in size, both within the individual preparations and from patient to patient But in exceptional cases of mye-lomatosis there is only a negligible var- iation from cell to cell

On correlating the cytometric findings with the types of paraprotein it was found that the myeloma cells, on the average, were larger in patients having γ_{1-A} para

proteinaemia than in patients with paraprotein of other types (γ_{ss} and γ_{μ}). This is in accordance with the findings of Paraskevas et al. (18) using diameter measurements. These authors also found the myeloma cells of group γ_{1-A} to have a lower nuclear/cell ratio than the cells of group γ_{ss} and γ_{μ} paraproteinaemia. This could not be confirmed by the present studies, either by diameter measurements or by planimetric measurements.

While the mature plasma cell is generally characterized by a highly eccentric situation of the nucleus, the myeloma cells show a wide variation in the situation of their nucleus. Since the nuclear/cell ratio of the myeloma cell varies widely within the individual smear (as shown in the present study), the degree of eccentricity must be measured by a technique in which the measurement of eccentricity is independent of the nuclear size. This aim was approached by measuring from the centre of the nucleus to the 2 points on the periphery of the cell on the line through the centre of the nucleus and the nearest point of the cellular periphery (cf. fig. 1, dotted line). Since, however, it is difficult to judge the centre of the nucleus accurately, it was preferred to use the parameters NC and CN (cf. fig. 1) which can be measured accurately, and to use the expression $\frac{NC}{CN}$ (eccentricity index) as a measure of the eccentricity of the nucleus. The measurements have shown that the myeloma cell in the γ_{1-A} group has, on an average, a more centrally placed nucleus (higher eccentricity index) than the corresponding cell in the group of γ_{ss} and γ_{μ} paraproteinaemia.

Lastly, as mentioned above, it was found that in the γ_{1-A} group there are more myeloma cells with irregular cytoplasmic outlines than in the group of γ_{ss} and γ_{μ} paraproteinaemia. This agrees with the impression mentioned by Paraskevas et al. (18). Conceivably, this greater irregularity in the outlines of the myeloma cells may indicate that the cells of the γ_{1-A} group are more brittle than those of group γ_{ss} and γ_{μ} myelomatosis, so that they are more apt to be injured in the process of smearing.

In the present study the maturity, atypia, or polymorphism of the myeloma cells did not allow of a consistent characterization of a given smear owing to the marked variation between the individual cells. Furthermore, a pronounced divergence was often seen between the degree of maturity of the nucleus and of the cytoplasm within the individual cell. This asynchronism is extremely striking in most smears from patients suffering from myelomatosis (18). Without doubt, it affords the explanation of the marked differences between previous groupings of these patients on the basis of the morphology of the myeloma cells.

Summary

Cytometric studies of myeloma cells were done in smears from 33 patients with myelomatosis. The cytometry comprised planimetry as well as diameter measurements of 50 myeloma cells in each smear. This showed a marked variation in cellular and nuclear size, within the individual preparation as well as from patient to patient, although in a very few cases of myelomatosis there was a negligible variation in the size of the individual myeloma cells. By relating the cytometric findings to the type of paraprotein, it was demonstrated by both measuring methods that the myeloma cells are significantly larger in patients with γ_{1-A} paraproteinaemia

han in patients with paraproteinaemia of the γ_{ss} and γ_{μ} types considered together The study of the cells also revealed a significant difference in the situation of the nucleus and the outlines of the cells in the two groups of paraproteinaemia, the myeloma cell of the group including γ_{ss} and γ_{μ} paraproteinaemia having on an average, a more eccentrically placed nucleus and a more regular cell outline than the myeloma cell of the γ_{1-A} group It is concluded that diameter measurements are applicable for relative cell measurements and reflect the absolute area of the myeloma cells

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Diagnostic Value of ^{131}I in Thyroid Disorders

A Study of 649 Patients

By

M O Dyrbye, E Pettersen and Th Friis

Since Hamilton and Soley published their studies in 1939 and 1940 (11, 12) numerous workers have tried to elucidate the function of the thyroid gland by use of radioactive iodide These investigations have shown that administration of a tracer dose of ^{131}I as sodium iodide, and measurement of the activity over the thyroid gland and in the serum, is frequently a very valuable diagnostic test in thyroid disorders (4 5 10, 13 15 18, 22)

Strange s thesis presented in 1959 (26) includes inter alia an excellent survey of the technique of ^{131}I studies and the various parameters which may be useful in diagnosing thyroid diseases His own studies however comprised only determinations of the 24 hour uptake and urinary excretion of ^{131}I

Usually the radioactive iodide is administered by mouth in doses of about 10 μC Thereafter the uptake in the gland is determined at the end of 3, 4, or 6 hours and again at the end of 24 hours and possibly also 48 hours At 24 hours the PB^{131}I in the serum is measured This represents the rate of hormone secretion from the gland According to Friis and Korsgaard Christensen (8) the 4 hour and 24 hour values of PB^{131}I are of particular diagnostic value

In order to ascertain whether a patient on thyroid medication is actually suffering from thyrogenic myxoedema, a thyrotrophin stimulation often has to be done, as in these patients the thyroid gland very seldom takes up iodide, even in the absence of myxoedema, because the glandular function is inhibited by the treatment (1, 6 14) As is well known, this stimulation test is also of interest in differentiating between thyrogenic and pituitary myxoedema

Another useful extension of the ordinary ^{131}I test is the L-triiodothyronine test In this country the value of this investigation has been studied by Friis (7) and by Ostergaard Kristensen et al (20a) It may be extremely helpful in diagnosing hyperthyroidism

Although there have been many investigations of the function of the thyroid

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Table I Classification of patients

	♂	♀	Total
Controls	17	106	123
Hyperthyroidism (untreated)	10	82	92
Hypothyroidism (untreated [3 pituitary])	3	23	26
Hypothyroidism (treated [1 pituitary])	3	15	18
Localized myxoedema	0	1	1
Acute thyroiditis	2	8	10
Hashimoto s goitre	0	3	3
Thyroid cancer	0	3	3
Exophthalmos (euthyroid [3 strumectomized])	0	16	16
Hypermetabolic (euthyroid)	12	14	26
Hypometabolic (euthyroid)	11	51	62
Diffuse atoxic goitre	16	99	115
Nodular atoxic goitre	5	35	40
Strumectomy (15 with goitre)	9	54	63
T_4 treated (euthyroid)	7	37	37
MTU treated (3 hyper , 5 eu thyr 2 hypothyr)	0	10	10
Still under observation	1	3	4
Total	96	553	649

gland, the individual series are fairly small Moreover, marked geographical differences have been found with respect to the uptake of radioactive iodine The present study was designed to investigate the value of the ^{131}I test in this country in a large series in which the results of the radioactive measurements were correlated with the patients' history, clinical and laboratory findings

Material

The material comprises a total of 649 patients 96 males and 553 females (cf table I) who were investigated during the period 1959—1961

The control group consists of 123 of these patients with no present or past signs of thyroid disorder whose basal metabolic rate ranged from — 10 to + 20 % The majority were suffering from nervous diseases or were admitted for physiotherapy

The patients of the various groups are classified by diagnosis which was based on the history, and clinical and laboratory findings In about 100 a definite diagnosis could not be made until after several admissions to hospital, and in 4 it was never established Patients who had undergone X ray examination using *iodized contrast media within the past year* were not included We also excluded patients who had received iodine-containing drugs, as these reduce the ^{131}I uptake by the thyroid gland and thus render the test unreliable (20)

Ninety-two patients had untreated hyperthyroidism, including 10 with nodular goitre, 57 with diffuse goitre, and 25 with no goitre, 24 had moderate exophthalmos, 2 severe exophthalmos, 66 none, and 11 had undergone thyroidectomy It was remarkable that 39 showed a heart rate of between 50 and 80 In other words the sign tachycardia was absent in not less than 42 % Two patients were *overweight and 31 underweight Overweight* is taken to mean a weight in kg above (height in cm less 100) + 10 %, underweight below (height in cm less 100 cm) — 15 %

There were 26 patients with untreated myxoedema of pituitary origin in three and post operative, following thyroidectomy, in one Four had diffuse goitre without exophthalmos, 8 were overweight, none under weight, and all had a heart rate ranging from *50—80*

Among the 18 treated myxoedematous patients one had pituitary and 5 post thyroidectomy myxoedema Three showed signs of *hypothyroidism, 1 had exophthalmos (following thyroidectomy)*, and none had goitre

The patient with localized myxoedema had severe exophthalmos and had been thyriodectomized The myxoedema involved both *lower legs B M R normal*

All the patients with subacute thyroiditis had goitres Among the 3 patients with Hashimoto s goitre (positive biopsy) one had a history of thyroidectomy All three patients with cancer had palpable goitres One had laryngeal paresis all had metastases to the cervical lymph nodes, but none distant metastases

Sixteen patients had exophthalmos and were designated as euthyroid Four of these patients had severe exophthalmos 2 had nodular and 5 diffuse goitre Only 3 had a history of thyroidectomy for hyperthyroidism In 15 of

these 16 patients the history indicated past hyperthyroidism

The series included 26 hypermetabolic and 62 hypometabolic patients without signs of present or past thyroid disorder, but with a B M R above + 20 % or below — 10 % None had goitre, a history of thyroidectomy or exophthalmos None was on thyroid medication

Among the hypermetabolic patients 6 were overweight and 13 underweight and among the hypometabolic ones 34 were overweight and 17 underweight

A total of 155 had non toxic goitre, nodular in 40 and diffuse in 115 None of these patients had been thyroidectomized had exophthalmos or was on thyroid medication

Thirty seven patients on thyroid medication had presumably never had myxoedema Sixteen were obese none underweight One had nodular goitre and one exophthalmos Three had a history of thyroidectomy

At the time of the study 10 were receiving methylthiouracil because of previous hyperthyroidism Of these patients 3 had thyrotoxic and 2 hypothyroid symptoms

Among the 4 patients admitted for evaluation 2 were suspected of having hyperthyroidism and 2 for hypothyroidism

Technique

The ^{131}I uptake measurements were carried out by the technique described previously (8) 4 and 24 hours after oral administration of ^{131}I 10—20 μC The PB^{131}I was determined 24 hours after the administration of ^{131}I on a precipitate obtained by adding 40 % trichloracetic acid to a blood sample and washing 3 times with equal parts of 10 % trichloracetic acid and a solution of potassium iodide The thyrotrophin stimulation test was performed by the technique described previously (6) According to Friis and Korsgaard Christensen the normal values for 4 hour uptake are 15—45 % and for the 24-hour uptake 30—70 % of the dosage In normal subjects the ^{131}I is less than 0 4 % of the dose per litre serum

Results

Control group As stated above this group comprised 123 patients between 15 and 75 years of age Incidentally, the age



Fig 1 Age distribution in the control group in the hyperthyroid and in the hypothyroid group

distribution in this group and in the un- treated hyper and hypothyroid patient: may be seen from fig 1 which shows tha in the control and hyperthyroid group the majority were between 40 and 50 while in the hypothyroid group the ag maximum was between 50 and 60 year:

The mean value of the B M R wa + 2 7 % 4 hour uptake 32 ± 14 7 % 24 hour uptake 51 ± 20 2 % and PB^{131} 0 09 % per litre serum 95 % of the pa tients had a 4 hour uptake from 5 to 65 % and a 24 hour uptake from 5 to 85 % o the dose As far as PB^{131}I is concerned only one patient (0 8 %) was abov 0 4 % Nine patients (7 5 %) were b tween 0 2—0 4 %

Figs 2 and 3 plot the 4 hour and 2 hour uptakes against age It will be see that no definite relationship was foun Others (9) have reported that the 2 ho and 6-hour uptakes decrease with advan ing age indicating decreasing thyro function

The *untreated hyper- and hypothyroid grou* as compared with the control group w be discussed in more detail (cf also fi 10—13) As regards the B M R (fig 1 the hyperthyroid patients had a me value of + 33 6 %, the hypothyroid or — 21 4 % Nineteen (22 %) hyperth roid patients had values below + 20 and one hypothyroid patient (4 5 %) value above — 10 % Ten hypothyr

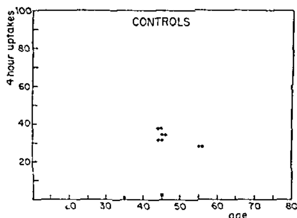


Fig 2 Relation between age and 4 hour uptake of ^{131}I by the thyroid gland as % of dose in the control group

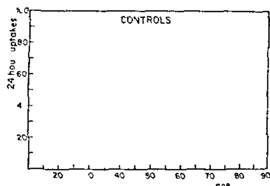


Fig 3 Relation between age and 24 hour uptake of ^{131}I by the thyroid gland as % of dose in the control group

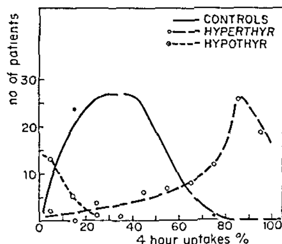


Fig 4 4 hour uptake of ^{131}I as % of dose Distribution among hypothyroid hyperthyroid and control groups

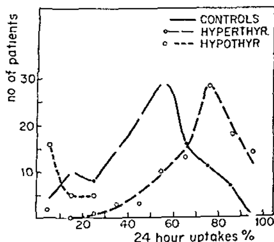


Fig 5 24 hour uptake of ^{131}I as % of dose Distribution among hypothyroid hyperthyroid and control groups

patients (45 %) had values ranging from — 20 % to — 10 %

At 4 hours the hyperthyroid and hypothyroid patients showed mean values of 73 3 % and 9 2 % (fig 11) Ten (12 %) hyperthyroid patients showed values below 45 % and five (19 %) hypothyroid patients had uptakes exceeding 15 % In fig 4 the distribution is set out graphically

The mean values of the 24-hour uptakes for hyperthyroid and hypothyroid patients were 71 9 % and 10 8 % According to fig 12, 31 (35 %) of the hyperthyroid patients had uptakes below 70 %, while no hypothyroid patient showed values exceeding 30 % In fig 5 the distribution is set out graphically It is apparent that between the hyperthyroid and the control groups the overlapping is greatest at 24 hours, between the hypothyroid and the control groups at 4 hours

In the case of PB^{131}I (fig 13) the mean values for hyperthyroid and hypothyroid patients were 1 22 % and 0 10 % respec-

ively per litre serum Thirteen hyperthyroid patients (15 %) had values below 0 4 % In the range 0 2—0 4 % there were 9 patients or 10 % On the other hand the hypothyroid patients did not differ from the control group, so that a lower limit cannot be fixed Fig 6 gives the distribution

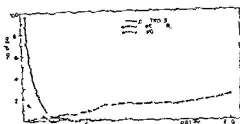


Fig 6 Distribution of PB¹³¹I as % of dose per litre serum (24 hours after administration) among the hypothyroid hyperthyroid and control groups

There was no relation between the 4 hour or 24 hour uptakes in these 3 groups of patients and their B M R (figs 7 and 8) or between the PB¹³¹I and the B M R (fig 9)

It is worth emphasizing, moreover, that no relation was found between the severity of the symptoms and the magnitude of the uptake or the PB¹³¹I This is in accordance with the observations of Schulz et al (23)

Figs 10—13 give the data for the various groups of patients (except patients with Hashimoto s goitre or thyroid cancer, patients treated with methylthiouracil and patients admitted for evaluation) As regards the B M R fig 10 shows that 3 of the treated myxoedematous patients had a considerably reduced B M R and that all patients with acute thyroiditis had a normal B M R Out of the euthyroid patients with exophthalmos 3 had an elevated and 2 a reduced B M R Six patients with non toxic diffuse goitre had elevated and 12 reduced B M R Three patients with non toxic nodular goitre had elevated and 5 reduced B M R Among the thyroidectomized patients the corresponding values were 5 and 9 and among the euthyroid ones treated with thyroid 0 and 16

The 4 hour uptakes (fig 11) showed the following besides what has been stated above 14 of the treated myxoedematous patients and 6 of the patients with thyroiditis showed values below 15 % The euthyroid patients with exophthalmos did not differ definitely from the control group, although there was a tendency to higher values (m = 43 6 %) Six (43 %) had uptakes exceeding 45 % and none below 15 %

The hypermetabolic and hypometabolic patients were on the same level as the control group (m = 31 4 % and 32 4 %) The patients with diffuse, non toxic goitre had a tendency to higher uptakes than the control group (m = 44 7 %), but the difference was not significant (48 or 43 % having uptakes exceeding 45 % and 11 or 10 % below 15 %) The patients with non toxic nodular goitre and the thyroidectomized patients showed uptakes like those of the control group On the other hand, all but 9 of the thyroidtreated, euthyroid patien s (25 %) had value below 15 % Essentially the same holds for the 24 hour uptakes (fig 12)

In all but one of the treated myxoedematous patients the 24 hour uptake was below 30 % Among the patients with acute thyroiditis 7 had values below 30 % Euthyroid patients with exophthalmos had a tendency to show values somewhat higher than in the control group (m = 57 0 %) The hypermetabolic and hypometabolic patients were distributed as in the control group while the non toxic diffuse goitres were on the whole somewhat higher (m = 58 2 %) The patients with

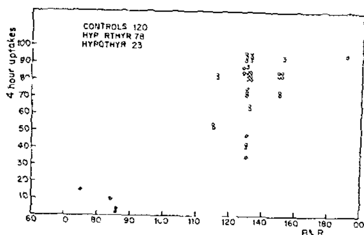


Fig 7 Relation between B M R as % of normal and 4 hour uptake of ^{131}I by the thyroid gland as % of dose

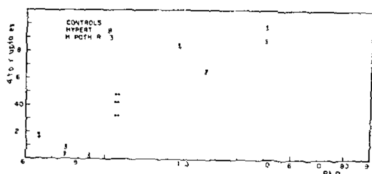


Fig 8 Relation between B M R as % of normal and 24 hour uptake of ^{131}I by the thyroid gland as % of dose

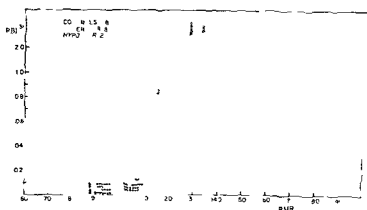


Fig 9 Relation between B M R as % of normal and PB^{131}I as % of the dose per litre serum

nodular, non-toxic goitre and the thyroidectomized patients were on the same level as the control group

The thyroid treated euthyroid patients had lower values than the control group (m = 19 4 %) except for 9 (25 %) who had uptakes exceeding 30 %

It may be mentioned that in the present study the uptakes in the hyperthyroid group did not appear to be correlated with the size or nature of the goitre or with the presence or absence of exophthalmos

Fig 13 gives the *PB^{131}I* values (24 hours after the administration) The values depend both upon the magnitude of the hormonal secretion and upon the stable iodine content of the gland, decreasing quan-

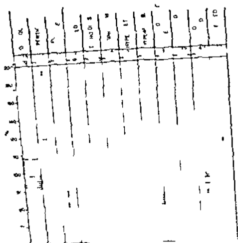


Fig 10 B M R as % of normal in the various groups of patients n = No of patients m = mean value ○ = in the exophthalmic group thyroidectomized ● = in the thyroidectomized group recurrence of goitre

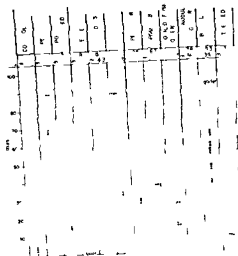


Fig 11 4 hour uptake of ^{131}I by the thyroid gland as % of dose in the various groups of patients Symbols as in fig 10

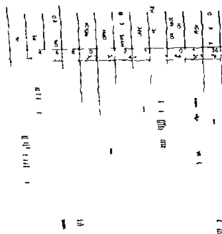


Fig 12 24 hour uptake of ^{131}I by the thyroid gland as % of dose in the various groups of patients Symbols as in fig 10

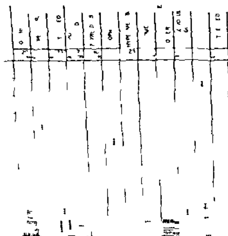


Fig 13 24 hour value of PB^{131}I per litre serum as % of the dose in the various groups of patients Symbols as in fig 10

tities of iodine entailing an increasing PB^{131}I Therefore the values are frequently higher following thyroidectomy as also reported by others (2 16 21) With a single exception all the treated myxoedematous patients and patients with acute thyroiditis had values below 0 4 % per litre serum On the other hand, 6 of the euthyroid patients with exophthalmos (38 %) had values exceeding 0 4 %/l se-

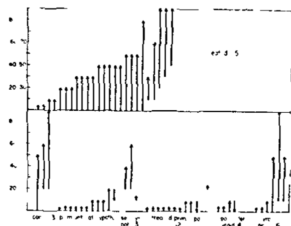


Fig 14 Thyrotrophin stimulation test Ordinate 24 hour uptake of ^{131}I by the thyroid gland The bases of the arrows indicate the uptake before stimulation, their tips the uptake after stimulation by 4 U S P units TSH

rum It must be mentioned, however, that 3 of the latter had a history of thyroidectomy Among the hypermetabolic patients none exceeded 0 4 %, while among the hypometabolic subjects 2 had greatly elevated values We have no explanation of this finding In the groups of non toxic goitre several patients had PB^{131}I values exceeding 0 4 %/l serum (6 or 5 % and 6 or 15 % respectively) In the thyroidectomized group (m = 0 31 %) 12, or 20 %, exceeded 0 4 % All but one of the thyroid-treated group were below 0 4 % There was no relation between the interval from thyroidectomy until the time of the study and the size of the PB^{131}I

Among the groups with Hashimoto's goitre and thyroid cancer (each consisting of 3 patients) the following findings were made Two of the former group had reduced 4-hour and 24-hour uptakes, all had normal PB^{131}I and 2 reduced B M R In the patients with thyroid cancer the B M R was not determined All had normal uptakes

The patient with localized myxoedema, who also had severe exophthalmos and a history of thyroidectomy, showed a normal B M R and uptakes, but an elevated PB^{131}I, presumably because of the thyroidectomy and the exophthalmos

Out of the 10 patients who were on methylthioracil medication during the period of the study, 3 were hyperthyroid, 5 euthyroid, and 2 myxoedematous All 3 hyperthyroid patients, one of whom had a normal B M R, showed increased 4-hour and 24 hour uptakes and PB^{131}I values exceeding 0 4 %/l serum Of the 2 hypothyroid patients, one of whom had a low B M R, one had a reduced uptake and a low PB^{131}I, while the other had high uptakes and a high PB^{131}I Of the 5 euthyroid patients (all with normal B M R) 2 had high uptakes and 3 an elevated PB^{131}I

Altogether, it must be said that ^{131}I findings in patients on antithyroid medication are extremely variable and do not afford data of clinical interest, as also reported previously (6, 7)

Among the entire series, 64 patients had thyrotrophin stimulation tests, using 4 U S P units of thyrotrophic hormone (fig 14) Three controls showed a marked elevation of the 24-hour uptake Among the patients with primary, untreated myxoedema (a total of 11) the uptake increased by less than 10 % of the dosage in 6, by 10—20 % in 3, and by 20—30 % in one, without ever reaching the normal range In one the uptake fell Among the 3 untreated patients with pituitary myxoedema 2 showed a marked increase, while one showed no increase None of the treated myxoedematous patients showed an increase beyond 20 % Among the 6 patients with acute thyroiditis 3 showed a marked increase and 3 no or only a slight (less than 20 %) increase Among 25 patients treated with thyroid, who had presumably never had myxoedema, 4

wed no or only a slight increase -se 4 patients had been on thyroid dication for many years

scussion and conclusion

The mean values for the ^{131}I uptakes in e 123 control patients (31 9 % and 3 % for the 4 hour and 24 hour up kes) were identical with Strange s (26) ean value for the 24 hour uptake (53 atients) and Friis and Korsgaard Chris- nsen's (8) experience (31 7 % and 4 6 %) However, the standard devia- ion was greater in the present series If t is demanded that 95 % of the patients e in the normal range this must be 5— 5 % for the 4 hour uptake and 5—85 % or the 24 hour uptake Strange found the orresponding values for the 24 hour up- take to be 29 6 and 72 4 % These normal ranges however, cannot be used without causing very pronounced overlapping of the hypothyroid and hyperthyroid groups We therefore preferred to reckon the normal ranges as 15—45 % and 30—70 % for the 4 hour and 24 hour uptakes as has been done hitherto These ranges included about 68 % of the control pa tients In Friis and Korsgaard Christen sen s series about 20 % and in Strange s 10 % were outside the normal range

A comparison of our overlapping with that found by others shows that among the hyperthyroid patients 12 % had 4-hour uptakes below 45 % and not less than 35 % had 24 hour uptakes below 70 In Friis and Korsgaard Christen sens (8) series the overlapping was less marked viz 9 % and 26 % and in Strange s series 4 2 % for the 24-hour up-take (the limit being 65 % and not 70 %) Thus while the 24 hour uptake in our hands is poorer than in other Danish se ries and virtually inapplicable as the only test for diagnosing hyperthyroidism, the 4 hour uptake tests are better suited, and in accordance with e g Clarke et al (3) and Ibarra (13)

In diagnosing hypothyroidism the 24 hour uptake tests gave good results in our hands none of the 26 patients having val ues exceeding 30 % This is considerably better than in the two previously reported Danish series (8 26) which, however comprised only a small number of pa tients On the other hand, the 4 hour up take tests were poorer, 19 % of the pa tients showing values in excess of 15 % Other authors have stressed that 24 hour measurements are better suited than measurements made sooner after the ad ministration of the isotope (13)

The PB^{131}I determinations consider ably increase the value of the radioactive tests in diagnosing hyperthyroidism, while they are worthless in myxoedema Only one patient in the control group showed a value exceeding 0 4 % Among the hyperthyroid patients 15 % had val ues below 0 4 % If 0 3 % is set as a limit, it will be seen that 3 % of the controls had higher and 8 % of the hyperthyroid patients lower values 8 % of the control group was above 0 2 % and 5 % of the hyperthyroid group below Therefore, 0 3 % must be the limit which affords the most favourable separation In series from other countries (3, 18 25) the 0 4 % limit is used, not 24 but 48 hours after adminis tration of the isotope As far as the other groups are concerned, a lowering of the normal limit from 0 4 % to 0 3 % means that 9 % of the hypermetabolic patients 8 % of those with diffuse non toxic goitre 20 % of those with nodular, non-toxic goitre and 26 % of those with a history of thyroidectomy have values ex ceeding 0.3 %

The fact that the normal limits in the present series are higher than in American materials is merely pointed out, as previous Danish publications have accounted for the higher normal uptake in this country

The following findings from the other patient groups will be emphasized

We were unable to reproduce the finding of Friis and Korsgaard Christensen (8) that patients with non-toxic diffuse goitres have higher ^{131}I uptakes In the present series this category hardly showed any difference in this respect from the controls This is in keeping with Strange's results (26) It is of interest, moreover, that only 26 % of the thyroidectomized patients had elevated PB^{131}I values Several workers are of the opinion that this percentage is higher That the 3 patients with Hashimoto's goitre had normal PB^{131}I values is at variance with the results of Murray et al (19) who often found the PB^{131}I value to be elevated in this type of case On the other hand, the finding that patients with acute thyroiditis often have a low uptake is in accordance with the experience of McConahey et al (17)

The thyrotrophin stimulation test, performed on 64 patients, showed results in accordance with previous studies on this subject (1, 6, 14), except for the fact that one patient with thyrogenic myxoedema showed some increase and that one patient with pituitary myoxedema failed to show an increase, presumably because the gland had undergone atrophy That half the patients with acute thyroiditis showed increased uptakes is at variance with the experience of Skillern et al (24) The reason why 4 thyroid treated patients, who had presumably always been euthyroid, did not respond is possibly atrophy of the gland due to the long-lasting thyroid medication

Summary

The uptake of ^{131}I by the thyroid gland 4 and 24 hours after oral administration of the isotope was studied in a total of 526 patients having various thyroid disorders, and 123 control patients The PB^{131}I was determined 24 hours after the administration of the isotope

The following normal ranges were found 4-hour uptake 32 % ± 14 7 % (about 15—45 %) 24-hour uptake 51 % ± 20 2 % (about 30—70 %), and PB^{131}I below 0 3 % per litre serum While about 32 % of the control patients were outside the normal range for the uptakes, only 3 % had PB^{131}I values exceeding 0 3 % per litre serum

Among the 92 hyperthyroid patients 12 % had 4-hour uptakes lower than 45 %, and 35 % had 24-hour uptakes lower than 70 % As regards PB^{131}I 8 % were below 0 3 % per litre serum

Among the 26 myxoedematous patients 19 % had a 4 hour uptake exceeding 15 %, while none had uptakes exceeding 30 % 24 hours after the administration of the isotope On the other hand, the PB^{131}I test was worthless in this group

In other words, in diagnosing hyperthyroidism the 4 hour uptake and the PB^{131}I are of importance and in diagnosing hypothyroidism the 24-hour uptake

Among the other groups of patients it was found that the uptake in the presence of non-toxic goitre was like that in the control group and that the PB^{131}I was elevated in about one quarter of the thyroidectomized patients

Acknowledgement

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Acute Renal Failure Due to Tubular Necrosis

Immediate Prognosis and Complications

By

MOGENS LUNDING IB STEINESS and JORN HESS THAYSEN

It is the purpose of the present paper to demonstrate the immediate prognosis and the frequency of uremic complications in a consecutive material of patients with acute renal failure due to tubular necrosis

Material and methods

Patients

Number of admissions The dialysis center at Rigshospitalet was set in operation on May 1st 1955 Being one of 4 centers in Denmark with a total population of 4 6 million it roughly covers a region with 1 million inhabitants In the period from May 1st 1955 to November 1st 1962 300 patients with acute uremia or with acute exacerbations in chronic uremia were admitted to the center and 228 hemodialytic treatments were carried out The annual average in the 7 1 2 year period was thus 40 admissions and 30 dialyses

The causes of uremia are listed in table I In the present paper we are concerned only with the 181 cases of acute renal failure arising in the course of some primary disease frequently — but not always associated with shock and characterized clinically by severe acute — usually oliguric — renal failure and histologically by tubular damage The terminology of this condition is confused but since the diagnosis tubular necrosis is in wide usage we have preferred this term although actual necrosis of tubular epithelium is rare

Treatment

The primary disease The primary diseases in our material are given in table II It can be seen that surgical cases represent the dominating causes of tubular necrosis In the center at Rigshospitalet the attitude towards the continued treatment of the primary diseases has become increasingly active over the years Radical operations or re-operations have been carried out early in the course of renal failure — if necessary after preoperative hemodialysis Further the indications for operations have become increasingly liberal since it has been noted repeatedly that the presence of uremia may suppress clinical symptoms of surgical diseases or operative complications in much the same way as corticosteroid therapy (2)

The renal failure Acute renal failure due to tubular necrosis in our material usually ran the typical course there being a pronounced oliguria lasting from a few days to 4 weeks followed by diuresis with moderately increased urine volumes and a slow but steady improvement in GFR During the oliguric phase the conservative treatment included *fluid restriction* to prevent overhydration (checked by daily weighings)

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Table I Causes of uremia in 300 patients, admitted over a 7 5 year period

1 "*Pre renal uremia* (chiefly sodium depletion)		12
2 "*Renal uremia*		259
Acute		
Tubular necrosis	181	
Acute glomerulonephritis	26	
Panarteritis nodosa	1	
Schonlein Henoch purpura	1	
Bilateral renal cortical necrosis	3	
Caval vein thrombosis	2	
Renal artery embolism	1	
Operative lesion of renal artery	1	
Myeloma kidney (i v urography)	1	
Traumatic kidney injury	1	
Uncertain	5	
Chronic		
Chronic pyelonephritis	26	
Chronic glomerulonephritis	3	
Nephrosclerosis	2	
Amyloidosis	2	
Myeloma kidney	2	
Oxalosis	1	
3 *Post renal uremia* (chiefly ureteral obstruction)		29
		Total 300

Table II The primary disease precipitating renal failure in 181 cases of tubular necrosis

"*Surgical cases*		124 (69%)
Post traumatic	15	
Biliary tract disease	43	
Others	66	
"*Medical cases*		37 (20%)
Nephrotoxins	8	
Coronary thrombosis	7	
Septicemia	6	
Narcotic poisoning	5	
Hepatic coma	3	
Hemolysis	3	
Others	5	
Obstetrical cases		20 (11%)
Post partum	16	
Post abortem	4	
		Total 181 (100%)

Hyperpotassemia was combated by oral (or rectal) *resin administration* (Resonium ®) and/or by the intravenous injection of hypertonic glucose, and severe anemia was treated with packed red cells The patients were *mobilized* as early as possible If this was not feasible, ambulatory exercises were made in bed conducted by the physiotherapist *Administration of calories and protein* has changed over the years Due to the risks involved (infection thromboembolism) intracaval infusion of 50 per cent glucose was given up after 1 years trial Consequently we gave as much glucose as the patients would volunteer to take perorally or as peripheral veins could tolerate (an average of 400 glucose Cal could be given per day in this way) In latter years we have, whenever possible, used diets with higher calorie contents and restricted amounts of protein in order to prevent the cachexia ensuing from the above mentioned low calorie, protein free regimen *Anabolic steroids* (chiefly Durabolin in a dose of 50 mg i m per day) were used quite extensively in the present material They proved to be effective in retarding the rise in serum urea in a limited group of patients, perhaps chiefly in women with obstetrical complications In the hypercatabolic ' traumatized or newly operated patients there was no detectable response to treatment (10, 17, 18)

Hemodialyses were carried out with three different types of apparatus, used in succession over the 7 1/2 year period All machines were equipped to remove fluid by ultrafiltration, if this was necessary on account of over hydration A blood pump was used with all three types

1) *Alwall apparatus* Urea clearance 90—120 ml/min at blood flows of 500—800 ml/min (May 1955 to Aug 1958)

2) *Kolff disposable twin coil kidney* (Freiburg Model) Urea clearance using two units in parallel 150—180 ml/min at blood flows of 500—800 ml/min (Aug 1958 to Dec 1961)

3) *Skeggs Leonards apparatus* in Brun s modification (produced by Ole Dich Copenhagen) Urea clearance with 24 layers 300—

400 ml/min at blood flows of 500—800 ml/min (Since Dec 1961)

A few dialyses were carried out with catheters in artery and vein on the arm but most were performed between the inferior vena cava (output), which was catheterized via the saphenous vein and a peripheral vein on the arm (return) Plastic catheters were used

Hemodialysis was initially performed when ever serum urea exceeded 400 mg/100 ml In the year from Nov 1961 to Nov 1962 the critical limit was decreased to 300 mg/100 ml Dialysis was further carried out — irrespective of the concentration of urea in the serum — when a patient was admitted in severe over hydration in order to remove excess fluid by ultrafiltration and in case hyperpotassemia could not readily be controlled by conserva tive measures (this proved to be a rare in dication there being among our 181 cases only one patient who had to be dialysed on account of a hyperpotassemia which could not be controlled by resins)

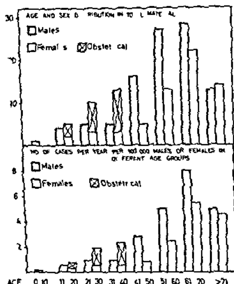


Fig 1 Age and sex distribution of 181 cases of tubular necrosis

Calculations

The severity of the uremia was evaluated by the length of exposure (the duration of oliguria) and by its intensity (average serum urea during oliguria)

The delineation between the oliguric phase and the diuretic phase of acute renal failure is not sharp In the not too hypercatabolic patient with average rates of urea production a spontaneous drop in serum urea from the 300—400 mg/100 ml level (our indication for dialysis in the present material) usually ensued at the time — or soon after the time — when 24 hour endogenous creatinine clearance exceeded 5 ml/min Somewhat arbitrarily this clearance level has therefore been used in the present paper to distinguish between the *oliguric phase* (*retention phase*) characterized usually by small urine volumes slow improvement of renal function and a gradual rise in serum urea concentration and the *diuretic phase* (*excretory phase*) characterized by rapidly increasing urine volumes more rapid improvement of renal function and a gradual decrease in serum urea concentration

The duration of the oliguric phase as defined above was calculated as the number of days during which 24 hour endogenous creatinine clearance remained below 5 ml/min

The average serum urea concentration during the oliguric phase was calculated as the sum of the daily measurements of serum urea during the oliguric phase divided by the duration of the oliguric phase in days On the days when dialyses were performed the highest (pre treatment) serum urea was used for the calculations In the tables to be shown in the following the term *mean serum urea* represents the mean value for the individual average serum urea concentrations within a group of patients

Results

General description of the material

The age and sex distribution The material comprises 181 patients (average age 53 years) 99 men (average age 55 years) and 82 women (average age 52 years) The age and sex distribution is shown in fig 1 the age range being from 3 to 81 years Apart from a preponderance of female patients in the age groups 21—40 years (20 obstetrical cases) it

Table III Total material of 181 patients divided into risk groups according to the nature of the primary disease precipitating renal failure (for details see text)

Diagnosis	No of pat	Average age (yrs)	Average duration of oliguria (days)	No dead	Mortality (%)
Risk group I					
Hemolysis	3	48	11	0	0
Nephrotoxins	8	37	10	1	13
Narcotic poisoning	5	39	5	1	20
Post partum or abortem	20	30	10	2	10
Total	36	34	9	4	11
Risk group II					
Trauma without severe cerebral damage	9	39	12	1	11
Trauma with severe cerebral damage	6	54	8	6	100
Benign biliary tract disease *radically operated*	19	60	11	5	26
Benign biliary tract disease, not radically operated or unoperated	18	63	11	15	83
C pancr et choledochi	6	67	10	4	66
Gastric surgery	14	60	8	9	64
Acute abdomen (excluding biliary tract)	14	60	10	7	50
Colonic surgery	7	68	9	3	43
Urinary tract surgery	13	59	10	4	31
Gynaecol *surgery*	5	62	7	3	60
Vascular surgery	5	55	14	2	40
Cardiac surgery	3	41	6	2	67
Neurosurgery	3	53	10	2	67
Others	2	68	10	2	100
Total	124	59	10	65	52
Risk group III					
Thrombosis art coron	7	64	10	6	86
Coma hepaticum	3	48	6	3	100
Tetanus septicemia etc.	6	59	16	6	100
Others	5	49	11	4	80
Total	21	57	12	19	90
Grand total	181	53	10	88	49

can be seen that tubular necrosis occurred with increasing frequency with age in both sexes If one excludes the obstetrical cases, the disease was somewhat rarer among women (62 cases) than among men (99 cases) and appeared to

occur at a somewhat later age in the women (average age of 62 patients 59 years) than in the men (average age of 99 patients 55 years) This finding is due to the fact that most of the primary illnesses that precipitate renal failure are prevalent among men and among the higher age groups (table III)

The nature and severity of the primary illnesses are shown in tables II and III Table II shows that surgical cases (post traumatic cases post operative cases and cases caused by acute surgical emergencies) were prevalent Among these biliary tract disease was dominating The primary diseases were of widely varying severity, ranging from mild and — apart from renal failure — essentially uncomplicated conditions (such as i a obstetrical cases) to very severe and complicated diseases (extensive trauma severe myocardial infarction, profound hepato-cellular failure etc) In table III the material has been divided into three risk groups according to the nature of the primary disease

Risk group I (good risks) comprises cases of acute renal failure following obstetrical conditions intravascular hemolysis and intoxications with nephrotoxins and narcotic poisons In this group the primary disease was potentially reversible and it was frequently under complete control requiring no further treatment, at the time of transfer of the patients to the dialysis unit

Risk group II (dubious risks) comprises cases of acute renal failure following acute surgical emergencies surgery or trauma In this group the primary disease was often very severe sometimes irreversible and it generally dominated the condition at the time of transfer to the dialysis unit requiring surgical intervention or interventions

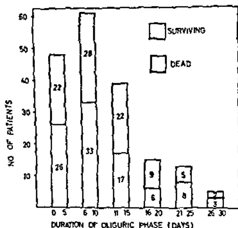


Fig 2 Duration of oliguric phase in 181 cases of tubular necrosis (for details see text)

Risk group III (poor risks) comprises cases of acute renal failure following extensive coronary thrombosis with shock, marked hepato cellular failure, septicemia, tetanus etc The primary disease was very severe and dominated the condition throughout the patient s admission to the dialysis center

The primary diseases were treated as actively as possible concurrently with the management of the uremia and its complications Thus 51 of the 124 patients in group 2 were operated or re operated after transfer Excluding minor surgery, such as catheterization of vessels and tracheotomies a total of 24 operations and 38 re operations were carried out in the entire material (mostly in risk group II) some of the patients being operated upon more than once Fourty two of the 62 operations (68 %) were carried out in the oliguric phase, in 21 cases following a pre operative hemodialysis

The severity of the renal lesion as expressed by the duration of the oliguric phase is shown in fig 2 The white columns show the duration of the oliguric phase in 93 surviving patients The

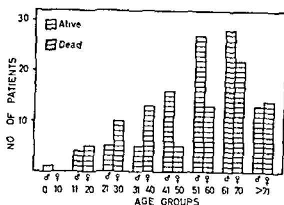


Fig. 3. Mortality according to age and sex in 181 cases of tubular necrosis.

superimposed black columns illustrate the duration of the oliguric phase in 13 deceased patients, who died following resumption of diuresis, and the duration from onset of renal failure until death among 75 patients, who died during the oliguric phase. The average duration of oliguria was 10 days in both groups. The range was from 3 days to 30 days.

Eighty-four of the 181 patients were dialysed with a total of 154 hemodialyses. The number of dialyses in the individual patient ranged from one to six. The effectiveness of the dialytic treatment can be evaluated by the mean serum concentration during oliguria in the dialysed patients. The mean serum urea concentration decreased over the years from 361 to 229 mg/100 ml due to the use of more and more effective dialysers and due to the decrease in the critical limit of serum urea used as indication for dialysis (table IV).

Table IV. Mean serum urea during the oliguric phase of dialysed patients in the reduced material (for definition see text) during the 7.5 year period May 1955 to Nov. 1962.

Year	No. of pat.	Mean serum urea (mg/100 ml)
8/12 1955	3	361
1956	3	295
1957	11	267
1958	10	282
1959	9	270
1960	14	267
1961	13	260
10/12 1962	14	229
7.5 years	77	266

Mortality

The overall mortality in the entire material was 88/181 = 49 per cent. Seventy-five of the 88 deceased patients (85 %) died during the oliguric phase. Thirteen patients (15 %) died between 4 and 26 days after resumption of diuresis from complications of various types, chiefly infectious, thromboembolic and cardiovascular.

The mortality in relation to age and sex is illustrated in fig. 3. The mortality in the age groups above 51 years is 68/117 = 58 % and equal in both sexes (men 39/68 = 57 %, women 29/49 = 59 %). The mortality in the age groups below 50 years is 20/64 = 31 %, and quite different in the two sexes (men 13/31 = 42 %, women 7/33 = 21 %). Excluding the 20 obstetrical cases, which have a singularly favorable prognosis, the overall mortality below 50 years is higher (18/44 = 41 %) and the sex difference absent (men 13/31 = 42 %, women 5/13 = 38 %). Also primary diseases, other than obstetrical complications, have a more benign character in the younger age groups. Most cases of acute renal failure caused by intoxications, by hemolysis and by traffic accidents without cerebral damage are in this age group (cf. table III). The increasing mortality with age in our material thus cannot be

Table V Mortality in total material of 181 patients in relation to the condition of the patients on arrival at the dialysis center

Condition	No of pat	No dead within 24 hours	24 hour mortality (%)	Total dead	Total mortality (%)
Serum urea					
>300 mg/100 ml	66	6	9	44	67
<300 mg/100 ml	112	10	9	41	37
Unknown	3	2	—	3	—
Serum potassium					
>6 mEq/l	25	2	8	17	68
<6 mEq/l	154	14	9	69	45
Unknown	2	2	—	2	—
With overhydration	26	5	19	14	54
Without overhydration	155	13	8	74	48
With coma	33	11	33	28	85
Without coma	148	7	5	60	41
With shock	27	9	33	23	85
Without shock	154	9	6	65	42
With respiratory problems	29	9	31	25	86
Without respiratory problems	152	9	6	63	41

attributed exclusively to a decreasing tolerance to uremia with age, but is to a large extent due to other factors, among which an increasing severity of the primary diseases with advancing age plays an important role

The mortality in relation to the condition of the patients on arrival at the dialysis unit is illustrated in table V

It can be seen that a high serum urea and an elevated serum potassium on arrival at the dialysis center was associated with an increased overall mortality whereas the 24 hour mortality was not significantly affected No less than 34 out of the 84 dialysed patients (40 %) had to be dialysed within 12 hours of transfer chiefly on account of high serum urea — indicating an unreasonable delay in transfer

Complications such as coma (due either to the uremia or to the primary disease), and complications in treatment, such as overhydration were associated with a definite increase in 24 hour as well as in overall mortality The delayed mortality *in this group* is, to a large extent, due to the increased frequency of broncho pulmonary infections in comatose and previously overhydrated patients (see later) It is noteworthy in this context, that only a few of the unconscious patients had been intubated or tracheotomized before transfer Although frank aspiration of gastric contents to the lungs during transport is on record only in 2 cases silent aspiration may have occured in several instances

The highest 24 hour, and overall mortalities were observed in patients

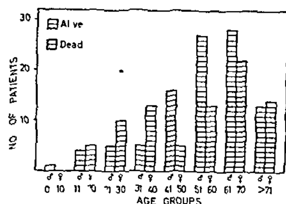


Fig. 3. Mortality according to age and sex in 181 cases of tubular necrosis.

superimposed black columns illustrate the duration of the oliguric phase in 13 deceased patients, who died following resumption of diuresis, and the duration *from onset of renal failure until death* among 75 patients, who died during the oliguric phase. The average duration of oliguria was 10 days in both groups. The range was from 3 days to 30 days.

Eighty-four of the 181 patients were dialysed with a total of 154 hemodialyses. The number of dialyses in the individual patient ranged *from one to six*. The effectiveness of the dialytic treatment can be evaluated by the mean serum concentration during oliguria in the dialysed patients. The mean serum urea concentration decreased over the years from 361 to 229 mg/100 ml due to the use of more and more effective dialysers and due to the decrease *in* the critical limit of serum urea used as indication for dialysis (table IV).

Table IV. Mean serum urea during the oliguric phase of dialysed patients in the reduced material (for definition see text) during the 7.5 year period May 1955 to Nov. 1962.

Year	No. of pat.	Mean serum urea (mg/100 ml)
8/12 1955	3	361
1956	3	295
1957	11	267
1958	10	282
1959	9	270
1960	14	267
1961	13	260
10/12 1962	14	229
7.5 years	77	266

Mortality

The overall mortality in the entire material was 88/181 = 49 per cent. *Seventy-five* of the 88 deceased patients (85 %) died during the oliguric phase. Thirteen patients (15 %) died between 4 and 26 days after resumption of diuresis from complications of various types, chiefly infectious, thromboembolic and cardiovascular.

The mortality in relation to age and sex is illustrated in fig. 3. The mortality in the age groups above 51 years is 68/117 = 58 % and equal in both sexes (men 39/68 = 57 %, women 29/49 = 59 %). The mortality in the age groups below 50 years is 20/64 = 31 %, and quite different in the two sexes (men 13/31 = 42 %, women 7/33 = 21 %). Excluding the 20 obstetrical cases, which have a singularly favorable prognosis, the overall mortality below 50 years is higher (18/44 = 41 %) and the sex difference absent (men 13/31 = 42 %, women 5/13 = 38 %). Also primary diseases, other than obstetrical complications, have a more benign character in the younger age groups. Most cases of acute renal failure caused by intoxications by hemolysis and by traffic accidents without cerebral damage are in this age group (cf. table III). The increasing mortality with age in our material thus cannot be

Table V *Mortality in total material of 181 patients in relation to the condition of the patients on arrival at the dialysis center*

Condition	No of pat	No dead within 24 hours	24 hour mortality (%)	Total dead	Total mortality (%)
Serum urea					
>300 mg/100 ml	66	6	9	44	67
<300 mg/100 ml	112	10	9	41	37
Unknown	3	2	—	3	—
Serum potassium					
>6 mEq/l	25	2	8	17	68
<6 mEq/l	154	14	9	69	45
Unknown	2	2	—	2	—
With overhydration	26	5	19	14	54
Without overhydration	155	13	8	74	48
With coma	33	11	33	28	85
Without coma	148	7	5	60	41
With shock	27	9	33	23	85
Without shock	154	9	6	65	42
With respiratory problems	29	9	31	25	86
Without respiratory problems	152	9	6	63	41

attributed exclusively to a decreasing tolerance to uremia with age but is to a large extent due to other factors among which an increasing severity of the primary diseases with advancing age plays an important role

The mortality in relation to the condition of the patients on arrival at the dialysis unit is illustrated in table V

It can be seen that a high serum urea and an elevated serum potassium on arrival at the dialysis center was associated with an increased overall mortality, whereas the 24 hour mortality was not significantly affected No less than 34 out of the 84 dialysed patients (40 %) had to be dialysed within 12 hours of transfer chiefly on account of high serum urea — indicating an unreasonable delay in transfer

Complications such as *coma* (due either to the uremia or to the primary disease) and complications in treatment such as overhydration, were associated with a definite increase in 24 hour as well as in overall mortality The delayed mortality in this group is to a large extent due to the increased frequency of broncho pulmonary infections in comatose and previously overhydrated patients (see later) It is noteworthy in this context, that only a few of the unconscious patients had been intubated or tracheotomized before transfer Although frank aspiration of gastric contents to the lungs during transport is on record only in 2 cases silent aspiration may have occured in several instances

The highest 24 hour and overall mortalities were observed in patients

Table VI *Mortality within different risk groups among dialysed and non dialysed patients of the total material of 181 cases*

	Dialysed			Non dialysed			Total material		
	No	Dead	Mortality	No	Dead	Mortality	No	Dead	Mortality
Risk group I	11	0	0	25	4	16	36	4	11
Risk group II	64	39	61	60	26	43	124	65	52
Risk group III	9	8	89	12	11	92	21	19	90
Total	84	47	56	97	41	42	181	88	49

who were in shock or who presented major respiratory problems on arrival to the dialysis center

It should be added in this context that while the condition of the patients when transferred influenced the mortality, the *transport distance per se appeared to be* unimportant

The mortality in relation to the nature of the primary disease is illustrated in tables III, VI and VII

In these tables the material has been subdivided into the three risk groups, as previously discussed

The mortality in the total material of 181 patients within the three risk groups *is 11, 52 and 90 per cent* respectively, not significantly ($p > 0.05$) greater among dialysed than among non-dialysed patients (table VI)

The post-traumatic cases (mostly traffic accidents) were almost all very severe with multiple fractures and lesions of various organs With only one exception the mortality did, however, entirely depend upon the presence or absence of severe brain injury, i e on the nature of the primary disease (table III)

In the "hepato-renal" cases the prognosis is very much influenced by the efficiency of treatment directed toward *the* primary disease In those patients, in whom the primary disease was radically treated before transfer or shortly after transfer (if necessary following pre operative hemodialysis), the mortality is significantly lower (26 %) than in patients with untreated or not radically treated primary disease (83 %) (table III)

All patients referred for treatment were accepted irrespective of the nature of the primary disease and irrespective of the patient's condition before transfer In order to evaluate the effectiveness of therapy it therefore appears reasonable to exclude from the total material

1) *Patients who died within the first 24 hours after transfer* This group includes 18 patients who were in irreversible shock or who had other severe complications in their primary disease on arrival at the center

2) *Patients in whom therapy was given up because the primary disease was intractable* This group of 9 patients includes the following patients a) 4 patients in whom a metastasizing, inoperable cancer was diagnosed after transfer as the cause of renal failure (3 biliary tract carcinomas, 1 mammary carcinoma with extensive metastases to the liver), b) 4 patients in whom extensive and irreversible brain damage was present at part of the primary disease (3 traffic accidents, 1 ischemic cerebral damage), c) finally therapy was abstained from in one patient

Table VII Mortality within different risk groups among dialysed and non-dialysed patients of the reduced material of 154 cases

	No	Age	Duration of oliguria	No of dia lysis	Mean serum urea (mg/100 ml)	Alive		Dead		Mortality
						No	Mean serum urea	No	Mean serum urea	
Dialysed patients										
Risk group I	11	35(±11)	17 5(±6)	22	270(±74)	11	270(±74)	0	—	0
Risk group II	58	55(±17)	14 5(±5)	111	264(±41)	25	258(±39)	33	269(±42)	57
Risk group III	8	56(±8)	17 8(±8)	13	270(±47)	1	192	7	281(±39)	87
Total	77	53(±17)	15 3(±6)	146	266(±48)	37	260(±54)	40	271(±41)	52
Non-dialysed patients										
Risk group I	22	33(±15)	6 2(±2 8)	0	150(±74)	21	149(±74)	1	182	5
Risk group II	47	60(±16)	6 6(±3 9)	0	186(±91)	34	177(±86)	13	210(±94)	28
Risk group III	8	60(±13)	8 5(±2 1)	0	255(±82)	1	323	7	245(±83)	87
Total	77	53(±20)	6 7(±3 5)	0	183(±88)	56	169(±84)	21	221(±86)	27
Grand total	154	53(±18)	10 9(±6 3)	146	224(±85)	93	205(±89)	61	254(±65)	40

Table VIII Mortality in the reduced material of 154 patients in relation to the duration of oliguria and the mean serum urea during oliguria

	Duration of oliguria (days)				
	0–5	6–10	11–15	>15	Total
No alive	26	33	17	17	93
Mean serum urea	125(±58)	214(±68)	248(±58)	280(±64)	205(±89)
No dead	6	20	20	15	61
Mean serum urea	156(±57)	245(±73)	279(±38)	269(±50)	254(±65)
Total no	32	53	37	32	154
Mean serum urea	131(±58)	226(±69)	265(±49)	275(±56)	224(±85)
Mortality (%)	19	38	54	47	40

who developed acute renal failure in terminal chronic pulmonary insufficiency

Table VII shows the results if these 27 cases are excluded from the total material of 181 patients The mortality among the 154 patients of the reduced material is 61/154 = 40 % 3 44 and 87 % respectively within the three risk groups and somewhat higher among dialysed than among non dialysed patients

The overwhelming influence of the *primary disease* (i e the risk group) on the mortality among the dialysed patients is evident from the fact that the severity of the uremia i e its duration (as estimated by the length of the oliguric phase)

Table IX *Frequency of uremic complications in relation to the duration of oliguria, and the mean serum urea during oliguria, in the reduced material of 154 patients (Mean serum urea within each group of duration of oliguria was calculated for patients with and without all of the 4 stated complications It was invariably found to be higher in patients with a complication than in those without a complication, but the standard deviations were considerable and the differences were not significant within the 5 % confidence limit)*

	Duration of oliguria (days)				
	0–5	6–10	11–15	>15	Total
Total no of pat	32	53	37	32	154
Mean serum urea (mg/100 ml)	131(±58)	226(±69)	265(±49)	275(±56)	224(±85)
No (%) with septicemia	1 (3)	3 (6)	4 (11)	9 (28)	17 (11)
No (%) with pulmonary complications	6 (19)	17 (32)	22 (59)	13 (41)	58 (38)
No (%) with cerebral complications	7 (22)	22 (42)	23 (62)	21 (66)	73 (47)
No (%) with gastro intestinal hemorrhage	0 (0)	3 (6)	7 (19)	8 (25)	18 (12)

and its intensity (as estimated by the mean serum urea concentration), is almost identical within the three risk groups

The mortality in relation to the severity of the uremia In the total material of 181 patients the mortality was virtually independent of the duration of the oliguric phase (cf fig 2), indicating that factors other than renal failure per se, *i e* the primary diseases, were chiefly responsible for the mortality Table VIII shows that the mortality in the reduced material of 154 patients increased with increasing duration of the oliguric phase and height of serum urea A detailed analysis of the cases, particularly within risk group II, shows that this finding is due only in part to an uneven distribution of more or less severe primary diseases in relation to the duration of renal failure Thus — although the overall mortality is dominated by the nature of the primary disease — the influence of the uremia cannot be overlooked as a contributing factor This is also apparent if one studies the frequency of severe uremic complications in relation to the degree of the uremia, and the increased mortality in patients with these complications

Complications

The complications in uremia were considered only for the reduced material of 154 patients, because a false picture of their frequency appeared to emerge if one included patients in whom therapy was given up (they were left to die from progressive uremia) as well as patients who died within 24 hours of transfer (they had been in renal failure for such a short period that the severity of the uremia, as defined by its duration and intensity, was less than the average for the total material)

Bacteriuria was present in 111 out of 125 patients in whom urine cultures were performed (89 %) Three patients developed clinical signs of acute pyelonephritis as a complication to the urinary tract

Table X Frequency of uremic complications in relation to the risk group in the reduced material of 154 patients

	Risk group I	Risk group II	Risk group III	Total
Total no of pat	33	105	16	154
No (%) with septicemia	3 (9)	13 (12)	1 (6)	17 (11)
No (%) with pulmonary complications	5 (15)	47 (45)	6 (37)	58 (38)
No (%) with cerebral complications	7 (21)	54 (51)	12 (75)	73 (47)
No (%) with gastro-intestinal hemorrhage	1 (3)	17 (16)	0 (0)	18 (12)

infection It should be mentioned that all patients had been catheterized and that most had an indwelling bladder catheter for longer periods of time

Infections in wounds for catheterization of vessels for dialyses was noted in most of the patients Usually it was of little significance but 3 patients developed septicemia, in all probability originating in the wound infection

Infection of wounds from surgical procedures was observed in 53 out of 93 operated patients (57 %) It was seen in 31 of 43 patients (72 %) with oliguria of more than 10 days duration and in 22 of 50 patients (44 %) with oliguria of less than 10 days duration

Rupture of abdominal wounds was observed in 14 of 79 laparotomized patients 18 %) Rupture was most frequent among patients who had infected wounds, who had been operated upon more than once who had pulmonary complications and who had oliguria of long duration with severe uremia

Septicemia If we leave out of consideration the 6 patients in whom septicemia was the primary disease precipitating renal failure septicemia occurred as a complication in 17 (11 %) out of 154 patients in the reduced material It occurred with increasing frequency with increasing duration of oliguria and increasing mean serum urea (table IX) and with somewhat higher frequency in group II than in group I and III, probably due to the fact that accidentally or surgically traumatized tissue represented a port of entry for bacteria (table X) The mortality among patients with septicemia was 7/17 = 41 %

Pulmonary complications The radiological picture of 'uremic lung was observed in 10 patients It was due to over hydration in all, and disappeared following dialysis with ultrafiltration Unless these patients later developed more extensive bronchopulmonary infections they are not included in the following discussion Patients with minor degrees of tracheobronchitis, not causing bronchial obstruction or impaired ventilation, and patients with small and insignificant radiological atelectases are also left out of consideration

Fifty eight out of the 154 patients of the reduced material (38 %) had major bronchopulmonary symptoms chiefly presenting the picture of pronounced tracheobronchitis with impaired ventilation, atelectases and/or bronchopneumonia Pulmonary symptoms of this type occurred with increasing frequency with increasing duration of oliguria and increasing mean serum urea (table IX), and they were somewhat more frequent among patients of group II than of group I and III (table X)

Laparotomy (with decreased diaphragmatic respiration), uremic cerebral symptoms (in particular various degrees of unconsciousness with insufficient coughing) and "uremic lung" appeared to predispose Thus pulmonary complications were seen in 37 out of 79 laparotomized patients but in only 5 of 33 patients of risk group I Pulmonary complications were seen among 50 of 85 patients who had various degrees of cerebral symptoms (due to the primary disease or to the uremia), but in only 8 out of 69 patients without such symptoms Finally, 7 of the 10 patients with the radiological picture of "uremic lung" later developed severe bronchopulmonary infection Tracheobronchial toilette was performed in 46 of the 58 patients, 17 were tracheotomized and 11 of the tracheotomized patients received mechanical and/or manual ventilation

Fourty of the 58 patients with pulmonary complications died (69 %) If the pulmonary complication had progressed to the point at which tracheotomy and ventilation was performed, the prognosis was exceedingly poor Fifteen of the 17 tracheotomized and ventilated patients succumbed

Cerebral complications (apart from those due to the primary disease, *i e* traumatic head injury and poisoning) occurred among 73 of the 154 patients = 47 % Thirty one patients had mild lethargy, 33 were in actual coma, 7 had episodes of psychosis and 5 presented convulsions (without evidence of overhydration) Three of the convulsing patients also presented one or more of the other cerebral complications The cerebral complications occurred with increasing frequency with increasing duration of renal failure and increasing mean serum urea (table IX) They also increased in frequency from group I to III (table X) Profound shock associated with the precipitating primary illness, severe infection and marked overhydration prior to transfer to the dialysis unit all appeared to predispose to cerebral complications EEG was performed only in 19 patients in the acute phase and showed varying degrees of abnormalities, mostly diffuse No single pattern characteristic for the uremic patient could be disclosed

Gastrointestinal hemorrhage was present in minor degrees in all uremic patients who had their stools examined for blood by chemical methods Profuse hematemesis, melaena or both occurred in 18 of the 154 patients of the reduced material (12 %) The symptom occurred with increasing frequency with increasing duration of the oliguric phase and increasing mean serum urea (table IX), and was particularly prevalent among the operated or traumatized patients of group II (table X) The mortality among the 18 patients with gastrointestinal hemorrhage was 10/18 = 56 %

Pericarditis was observed in 11 of the 154 patients of the reduced material (7 %) It was prevalent among patients with uremia of long duration (average duration 14 6 days) and with high serum urea (mean serum urea 297 mg/100 ml) Nine of the 11 patients died and showed at necropsy the typical picture of uremic pericarditis One patient had a 500 ml hemorrhagic effusion in the pericardium

Parotitis Moderate bilateral parotid swelling was not infrequent in patients with severe uremia Unilateral purulent parotitis was seen in 8 of the 154 patients in the reduced material (5 %)

Combined frequency of the major complications Most of the complications mentioned above occurred in combination in the same patient The sum of registered

complications is thus not equal to the number of patients with complications Major complications (septicemia, pulmonary complications, cerebral complications G I hemorrhage, pericarditis) occurred in 96 of the 154 patients with a mean oliguric phase of 12 6 days and a mean serum urea of 248 mg/100 ml The 58 patients free from major complications had a mean oliguric phase of 8 2 days and a mean serum urea of 188 mg/100 ml

The more effective dialytic treatment during the first 10 months of 1962 resulting in a decrease in mean serum urea from about 280 mg/100 ml before Jan 1st 1962 to about 230 mg/100 ml after that date (see table IV), apparently caused a reduction in the frequency of certain major uremic complications Thus, the frequency of gastrointestinal hemorrhage was reduced from 15/63 (24 %) to 0/14 and the frequency of cerebral complications from 42/63 (70 %) to 6/14 (43 %) whereas other complications (septicemia and pulmonary complications) occurred with unaltered frequency

Discussion

Despite the asset of centralized treatment including hemodialysis the mortality in patients with acute renal failure due to tubular necrosis is still high However the overall mortalities in different materials can hardly be directly compared because the composition of the materials varies considerably in particular with respect to the nature of the primary diseases precipitating the acute renal shut down (table XI)

In the observations in the present material a number of different factors contribute to this high mortality primarily problems related to the transfer of the patients to the dialysis center to the treatment of the primary disease and to the management of the complicating uremia

Transfer of the patients to the dialysis center It is apparent from our material (table V) that a high serum urea and an elevated serum potassium at transfer was associated with an increased overall mortality whereas the 24 hour mortality was not significantly affected — probably due to prompt dialytic treatment Thus, no less than 40 per cent of the dialysed patients in our material had their first dialysis within 12 hours of arrival

Complications in therapy, such as overhydration, and complications in uremia such as coma, were associated with a definite increase in overall as well as in 24 hour mortality This is mainly because bronchopulmonary infectious complications were prevalent among these patients Only a few of the comatose patients were intubated or tracheotomized before transfer Aspiration of gastric contents during transport occurred in at least two cases Our results call for intubation (or tracheotomy) to secure free air ways before transport in all comatose patients — a fact which we have apparently stressed too little to the referring hospitals

The highest 24 hour and overall mortalities were observed in patients who were in shock and who presented major respiratory problems on arrival at the dialysis center

The conclusion to be drawn from these findings is that transfer of the patients should be early guided by biochemical (and clinical) uremia rather than by the duration of oliguria and that necessary steps should be taken to secure safe transport to the dialysis center These include all measures to bring the patient out of shock, to secure free air ways and

Table XI Mortality in patients with tubular necrosis in different materials in relation to the nature of the primary disease precipitating renal failure (total non reduced materials are used)

References	Obstetrical complications			Hemolysis			Nephrotoxins and other intoxications			Surgical diseases Post operative complications			Post traumatic		
	No	Dead	Mortality (%)	No	Dead	Mortality (%)	No	Dead	Mortality (%)	No	Dead	Mortality (%)	No	Dead	Mortality (%)
Muirhall (1)	8	1	13	6	1	17	—	—	—	33	17	51	—		
Smith et al (15)	—	—	—	—	—	—	—	—	—	—	—	—	51	27	53
Russel (12)	34	8	24	—	—	—	—	—	—	—	—	—	—	—	
Palmer & Henry (9)	—	—	—	—	—	—	16	6	38	—	—	—	—	—	
Salisbury (13)	—	—	—	17	9	53	—	—	—	—	—	—	—	—	—
Gold et al (5)	—	—	—	—		—	20	5	25	—	—	—	—	—	—
Parsons & McCracken (11)	25	2	8	—	—		—	—	—	18	14	78	7	4	57
Bluemle et al (4)	16	4	25	24	7	29	9	5	55	32	23	72	6	5	83
Legrain et al (7)	216	21	10	64	16	25	4	8	19	71	46	64	38	26	68
Longridge et al (8)	20	4	20		—	—	7	2	29	—	—			—	—
Riley et al (6)	10	0	0	4	0	0	9	2	22	28	17	61	17	9	53
Shackman et al (14)	—	—	—				—	—	—	50	42	84	29	22	76
Balslov & Jorgensen (3)	16	3	19	3	1	33	64	28	44	177	111	63	7	6	86
Present material	20	2	10	3	0	0	13	2	15	109	58	53	15	7	47
Total	365	45	12	121	34	28	180	58	32	518	328	63	170	106	62

to combat by conventional conservative methods the two acutely life threatening complications of acute renal failure i e hyperpotassemia and overhydration

The primary disease and its treatment The influence of the primary disease on the mortality is evident from table XI which confirms our results in showing a relatively good prognosis in hemolytic toxic and obstetrical cases (our risk group I) as opposed to a very poor prognosis in surgical cases and post traumatic cases (our risk group II)

In our risk group I the mortality could be ascribed entirely to the primary disease precipitating renal failure The dialytic treatment was thus adequate to prevent death from uremia (table VII) although not to prevent the development of serious uremic complications in several of the patients (table X)

The high mortality in our risk groups II and III is doubtless partly due to the fact that some of the primary diseases were so severe that the patients would have died from the disease whether complicated by uremia or not This is applies to the post traumatic cases with severe brain injury most of the severe hepatic comas some of the cancers and a number of the coronary occlusions

It is nevertheless apparent that many of the primary diseases were potentially reversible and would not have entailed

either the high number of complications or the high mortality had not uremia ensued There are several reasons for this In patients with 'surgical diseases uremia may blur usual diagnostic signs and symptoms resulting in delay — sometimes critical — in diagnosis and operative treatment Uremia also causes delayed wound healing (resulting i a in leakage from surgical anastomoses), re duced resistance to bacterial invasion through the traumatized tissue and in creased disposition to post operative pul monary complications

That early and radical surgery on liberal indication may to some extent reduce fatalities due to such complica- tions is evidenced by our results in the hepato-renal cases following biliary tract disease Yet the mortality in the radically treated group is higher than in a similar group of patients with biliary tract disease uncomplicated by acute renal failure

The impression is therefore gained that our dialytic treatment was not adequate to prevent fatalities caused by the uremia in the surgical and post traumatic cases because these traumati zed patients are more liable to develop complications in their primary disease than the essentially non traumatized patients of risk group I

In conclusion it can be stated that the still high mortality in patients with tubular necrosis following surgical con ditions or trauma can be further reduced only by a combination of early and radical surgical intervention and dialytic treat ment carried out on very liberal indi cations Sound judgement as to whether operation or dialysis is more urgent should be exercised by the referring hospital before it is decided whether the patient should be operated before or after transfer to the dialysis center Consultation between the referring hos pital and the center is strongly advisable in all such cases

The management of the uremia and its complications There is little doubt from our results that dialytic management of uremia could not keep the patients in any of the three risk groups entirely free from uremic complications In the few other materials in which the frequency of complications is on record (3, 4, 16), it appeared to be about the same as in the present material In our material the frequency of complications was related to the severity of the uremia as estimated by its duration (length of oliguric phase) and its intensity (mean serum urea) Complications such as coma and gastro- intestinal hemorrhage were considerably reduced in frequency during the last year, when mean serum urea was consistently lower than in the foregoing years Further, like others, we have observed that many of the complications (in particular coma and gastrointestinal hem orrhage) were fully and rapidly revers ible in the individual patients if uremia was treated by effective dialysis

There is no reason to discuss in detail the treatment of these complications several of which can apparently be prevented by more effective dialysis Two facts are worthy of comment however

The high mortality among our patients with bronchopulmonary complications is due in large part to an unreasonable delay in tracheotomy and ventilation Coma laparotomies peritonitis thoracic trauma overhydration and pre existing pulmonary disease entail a liability to bronchopulmonary complications and such patients should be watched with particular care

Table XI Mortality in patients with tubular necrosis in different materials in relation to the nature of the primary disease precipitating renal failure (total non reduced materials are used)

References	Obstetrical complications			Hemolysis			Nephrotoxins and other intoxications			Surgical diseases Post operative complications			Post traumatic		
	No	Dead	Mortality (%)	No	Dead	Mortality (%)	No	Dead	Mortality (%)	No	Dead	Mortality (%)	No	Dead	Mortality (%)
Alwall (1)	8	1	13	6	1	17	—	—	—	33	17	51	—		—
Smith et al (15)	—	—	—	—	—	—	—	—	—	—		—	51	27	53
Russel (12)	34	8	24	—	—	—	—	—	—	—		—			—
Palmer & Henry (9)	—	—	—	—	—	—	16	6	38		—	—			
Salisbury (13)		—	—	17	9	53	—		—		—		—		
Gould et al (5)		—	—	—		—	20	5	25		—		—		—
Parsons & McCracken (11)	25	2	8		—	—	—	—	—	18	14	8	7	4	57
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Legrain et al (7)	216	21	10	64	16	25	42	8	19	71	46	64	38	26	68
Loughridge et al (8)	20	4	20	—		—	7	2	29	—		—	—		—
Kiley et al (6)	10	0	0	4	0	0	9	2	22	28	17	61	17	9	53
Shackman et al (14)	—	—	—	—		—			—	50	42	84	29	22	6
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It is nevertheless apparent that many of the primary diseases were potentially reversible and would not have entailed

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Gastrointestinal hemorrhage is a serious complication in acute renal failure, for several reasons The absorbed protein aggravates the uremia and the absorbed sodium and water induce overhydration, if blood loss has to be offset by transfusion of full blood on account of shock The hemorrhage may become accentuated if multiple transfusions have to be given, because hemorrhagic diathesis tends to occure on replacing blood loss by transfused blood, which is low in thrombocytes (and possibly also in other factors) For gastro-colonic hemorrhage due to uremia the only prophylaxis and treatment is effective dialysis, which usually results in complete arrest of severe hemorrhage within 24—48 hours

The conclusion to be drawn from our results is that the critical limit for dialysis should be reduced at least to 300 mg/100 ml in order to avoid serious uremic complications

Summary

Over a 7 1/2-year period 300 patients were admitted in acute uremia and 228 hemodialyses carried out in the dialysis center at Rigshospitalet, covering a region with about 1 million inhabitants

One hundred and eighty-one of the 300 patients had "tubular necrosis", following surgical conditions in 124 medical diseases in 37 and obstetrical complications in 20 The average duration of oliguria was 10 days with a range from 3 to 30 days Eighty-four of the 181 patients were dialysed with a total of 154 dialyses

The overall mortality was 88/181 = 49 per cent If 18 patients who died within 24 hours of transfer, and 9 patients in whom therapy was given up on account of irreversible primary disease, are excluded, the lethality in the remaining ("reduced") material was 61/154 = 40 per cent

The mortality depended on the condition of the patients at transfer, on the duration and intensity of the uremia and on the nature of the primary disease precipitating renal failure The latter factor was most important The material was divided into three risk groups 1) good risks, i e cases following obstetrical complications, intoxication and hemolysis, 2) dubious risks, i e cases following surgery, acute "surgical diseases" and trauma, and 3) poor risks, i e cases following coronary thrombosis, hepato cellular failure, septicemia, tetanus and other grave "medical diseases" The mortality in the total material was 11, 52 and 90 per cent, in the reduced material 3 44 and 87 per cent respectively within these three groups

Complications in uremia were observed with the following percentile frequencies cerebral symptoms 47, bronchopulmonary infection 38, rupture of abdominal wounds 18, gastrointestinal hemorrhage 12, septicemia 11, pericarditis 7 and parotitis 5 The frequency of these complications showed a definite relationship to the severity of the uremia as estimated by its duration (length of oliguric phase) and its intensity (mean serum urea during oliguria)

The findings are discussed with respect to practical measures which may further reduce the still high mortality Stress is laid on the importance of early transfer, of steps requisite for safe transport, of early and radical management of the primary disease (particularly in the surgical and post-traumatic cases) and of effective dialysis on liberal indication

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Koskela Municipal Geriatric Hospital, Helsinki, Finland

Is the Vitamin B_{12} Treatment of Pernicious Anemia a Predisposing Factor for Thromboses in Aged Patients?

By

Laija Klemetti

Pernicious anemia is generally known as a disease of middle aged and aged persons. When untreated it is reported to give complications also from the vascular system, e. g. angina like attacks and even suspected myocardial infarctions.

In the Koskela Municipal Geriatric Hospital we have during 2 years, met four peripheral vascular thromboses in patients treated for pernicious anemia with vitamin B_{12} (during the same period 35 pernicious anemia cases were hospitalized, 19 of these had not been previously treated). In one subject the thrombosis occurred immediately after the reticulocyte peak (case 2), in another 9 days after the reticulocyte peak (case 3) and in two cases approximately 2 months after the reticulocyte peak (cases 1 and 4).

Case reports

Case 1. Woman aged 75, bedridden since spring 1961. Admitted for examination and treatment Oct. 13 1961. History of cerebral vascular bleedings in 1959 and 1960. The patient is a sclerotic pale old woman with mitral stenosis and cardiac failure. A marked macrocytic anemia is discerned and bone marrow biopsy confirms the diagnosis of pernicious anemia. Treatment with vitamin B_{12} is started without delay, the blood count improves quickly and reticulocyte peak is observed within a week. Hb 3.85—8.95 g/100 ml, erythrocytes 1.20—3.41 mill./mm³, reticulocytes 0.8—14.5 %. The general condition remains, however, unchanged, the patient remains bedridden. Dec. 8 (55 days after the reticulocyte peak) the condition suddenly grows worse, with severe gastro-intestinal pain and vomiting. Exitus Dec. 12 1961. At autopsy a thrombosis of the cranial mesenteric artery is found.

Case 2. Woman aged 82, with a history of cardiac failure for several years and of diabetes and gall stones for 3 years. Since Feb. 1962 treated for nephritis which proved treatment resistant. Hospitalized May 14—June 25 1962, readmitted Dec. 17 1962. On admission general condition satisfactory, examination reveals palpation pain in the epigastric area which is considered due to pyelonephritis. During hospitalization the patient develops macrocytic anemia. Hb 8.0 g/100 ml, erythrocytes 2.12 mill./mm³ and sternal biopsy confirmes the diagnosis of pernicious anemia. Treatment with vitamin B_{12} is started Jan. 23 1963, the reticulocyte peak within a week 49—9.2 %, the blood count improves, erythrocytes 4.12 mill./mm³, Hb 12.1 g/100 ml. Feb. 1 1963 the patient has strong substernal pains, changes in ECG typical for myocardial infarction are observed and the GOT values rise from 17 to 89 SF units. The general condition gets worse and death ensues Feb. 14 1963. No autopsy.

Case 3. Woman aged 60, with a history of cerebral vascular accident at the age of 40

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The Department of Medicine (Head Carsten Muller, M D), Telemark Sentralsjukehus, Skien Norway

The Electrocardiogram in Patients with Previous Myocardial Infarction

By

NORMAN ANDERSSEN and OYVIND SKJÆGGESTAD

Information on electrocardiographic findings in patients with previous myocardial infarction is scarce and divergent Most textbooks on electrocardiography and internal medicine mention that the Q waves rarely may disappear Gittler et al (4) examined 51 patients 1 year following myocardial infarction In only one case was a normal electrocardiogram obtained whereas the rest had pathological Q waves Pappas (7) found normalisation of the electrocardiogram in 14 of 742 patients with previous myocardial infarction Bohm (1) on the other hand found electrocardiograms with normal or non specific patterns in 39 (26 %) of 150 patients examined 1—6 years after infarction According to Friedberg (3) normalisation occurs in 15 % of cases Woods et al (8) correlating autopsy findings with electrocardiograms found diagnostic electrocardiographic evidence of old infarction in only 19 of 50 cases

The varying findings may result from difficulty in defining diagnostic criteria Even if strict criteria are laid down for each single electrocardiographic lead the final diagnosis is often based upon the observer's personal judgment Davies (2) found that observer variation in interpreting the electrocardiogram caused considerable divergence of diagnosis, even when the interpreting was done by a single observer

The purpose of the present study was to examine how often the electrocardiographic signs of myocardial infarction persist, become equivocal or disappear Opportunity for this was offered by the fact that almost all surviving patients treated at the medical department for acute myocardial infarction were put on long term anticoagulant treatment and were seen regularly as out patients

Material and methods

Patients included in this study were treated for first time myocardial infarction in our medical department Whenever a recurrence of infarction occurred the patient was excluded from further study Apart from a small number of patients with whom contact was lost (mainly for geographical reasons), the material comprises all survivors from first time myocardial infarction seen in the 4 year period ending spring 1962 A total of 128 patients were examined at least once and as

Submitted for publication January 7 1964

thereupon slight derangement of speech and decreased muscular strength in right upper limb Admitted on social grounds June 25 1963 Routine examination reveals a macrocytic anemia, and vitamin B_{12} is started without delay The treatment is followed by a reticulocyte crisis 2,5—7 7 % and a steady improvement of the blood count Hb 7 9—13 1 g/100 ml and erythrocytes 2 15—3 75 mill /mm³ July 12 1963, 9 days after reticulocyte peak, a superficial venous thrombosis in left thigh is observed

Case 4 Woman aged 79, with fits of unconciousness since spring 1963 Admitted July 18 A severe macrocytic anemia is revealed Hb 5 7 g/100 ml, erythrocytes 1 28 mill /mm³ Bone marrow biopsy and Schilling test confirm the diagnosis of pernicious anemia Vitamin B_{12} treatment is started July 25, a reticulocyte peak 1 0—17 8 % as well as rapid improvement of blood values Hb 5 7—11 5 g/100 ml, erythrocytes 2 15—3 75 mill /mm³, is noted Sept 28 (61 days after the reticulocyte peak) the patient suddenly collapses, ECG shows a picture typical of anterior myocardial infarction Exitus letalis Sept 30 1963 At autopsy a fresh extensive anterior infarction is found, besides a strong general atherosclerosis

Discussion

The treatment of pernicious anemia with vitamin B_{12} is considered to be safe Allergic reactions, which were common in connection with liver extract injections, are absent during vitamin B_{12} treatment Manifestation of polycythaemia vera during B_{12} treatment has been reported by Hinz (3)

According to the literature the occurrence of thromboses in aged persons treated for pernicious anemia with vitamin B_{12} has not been studied It seems, however, quite likely that thromboses could occur, since old age as such is a pre disposing factor for cardiovascular accidents, and, on the other hand, the hemodynamic changes which take place during the recovery from anemia (1,4) doubtless increase the risk of vascular complications A superimposed change in the blood coagulation system during the treatment may play a role both the prothrombin value (2) and the thrombocyte count of the blood are reported to show an increase during vitamin B_{12} treatment

Common to all the cases reported is the occurrence of thromboses after the onset of treatment with vitamin B_{12}, at a time when the red blood count still was rising, though the time interval from the reticulocyte peak varied from case to case Another common feature is a previous history of cardiovascular disease, which probably is a strong predisposing factor for vascular complications The present cases allow no conclusions as to the frequency of thromboses during treatment of pernicious anemia with vitamin B_{12} Nevertheless it seems that, when treating old patients with vitamin B_{12}, one should specially look out for any signs suggestive of incipient vascular complication

Summary

Four cases of peripheral vascular thrombosis in aged patients shortly after the reticulocyte peak due to vitamin B_{12} treatment of pernicious anemia are reported Common to all the patients is a history of cardiovascular symptoms Consideration is given to the risk of vascular accidents during the treatment of pernicious anemia when changes in blood clotting system and hemodynamics occur

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Table I Distribution according to age, sex and electrocardiographic findings in the acute stage of myocardial infarction in 128 patients submitted to electrocardiographic follow-up examination

ECG in acute stage	No of pat	Sex		Age		Time elapsing from infarction to ECG checking		
		♂	♀	Range	Mean	1/2 year (4–8 months)	1 year (9–15 months)	2 years (18–36 months)
Unequivocal signs of infarction (group 1)								
Anterior (Q in I aVL or V_{1-6})	53	48	5	33–79	60	27	30	23
Posterior (Q in II III, aVF)	52	42	10	39–78	61	29	28	17
Equivocal or no signs of infarction (group 2))	23	20	3	44–82	61	7	20	13

close to 1/2, 1 and 2 years following the infarction as possible (table I)

According to findings in the acute stage, the material was divided into two groups

1) One hundred and five patients with *unequivocal electrocardiographic signs of infarction* Eighty four of these patients had SGOT determined within 4 days of infarction all having values above 40 units

2) Twenty three patients with *pathological electrocardiograms, but with equivocal or no signs of infarction* All patients in this group had increased SGOT activity (above 40 units) as well as other laboratory evidence of infarction (fever, leucocytosis, increased ESR)

The ECGs were recorded with a Cardiopan 3 and the following 12 leads obtained Extremity leads I, II, III, aVR, aVL and aVF, and precordial leads V_1-V_6 At the follow up examination the electrocardiographic findings were classified as follows *A ECGs with persisting unequivocal signs of infarction* Pathological Q waves in doubtful cases supplemented by ST T changes were considered as evidence of infarction Criteria of infarction were adopted from Lipman and Massie (5) and Massie and Walsh (6) *B ECGs with equivocal signs of infarction* Above mentioned criteria were not met in this group, but the ECGs did not exclude the possibility of previous infarction *C ECGs with no signs of infarction*

Results and discussion

The difference between ECGs obtained at 1/2 year and 1 year following infarction (35 patients) were mainly restricted to the ST-T-segment In no case did the difference between the two examinations justify alteration of classification according to the above-mentioned groups A, B and C This was also true of the 31 patients examined 1 year and 2 years after the infarction In the present material, therefore, changes of diagnostic importance did not appear in the ECG between 1/2 year and 2 years following infarction Accordingly, any regression of the electrocardiographic signs of infarction occurs mainly within the first 1/2—1 year Bohm (1), who examined patients 1—6 years following infarction, found that the final electrocardiographic pattern was established after 1 year

The changes in the ECGs that have occurred from the acute stage of infarction to the first follow up examination 1/2—2 years later are seen in table II In 17 (16 %) of the 105 patients with

Table II Electrocardiographic findings in 128 patients 1/2—2 years after myocardial infarction (groups A B and C) in relation to findings in the acute stage (groups 1 and 2)

ECG at follow up examination	ECG proved infarction (group 1)			Non diagnostic ECG (group 2)	Total
	Posterior	Anterior	Total		
A Unequivocal signs of infarction	41	47	88	—	88
B Equivocal signs of infarction	8	5	13	11	24
C No signs of infarction	3	1	4	12	16
Total	52	53	105	23	128

unequivocal electrocardiographic evidence of infarction in the acute stage (group 1), the ECG had changed to such an extent that the previous infarction could not be diagnosed with certainty This was caused by more or less normalisation of the ST T segment combined with the appearance of rudimentary r waves or reduction in Q waves to within normal size In patients with posterior infarction groups B and C would possibly have been larger if the ECGs had been recorded during deep inspiration and thus caused a greater reduction in Q_{III}

In no case was a completely normal ECG obtained at the follow up examination from a patient with unequivocal electrocardiographic evidence of infarction in the acute stage

Among patients with equivocal or non diagnostic ECGs in the acute stage (group 2) 11 had equivocal signs of previous infarction (17 in the acute stage) In 12 there were no signs of infarction (6 in the acute stage) and in 3 of these the ECG had become normal As expected the tendency towards normalisation was greatest in this group of patients

In the whole series 40 or 31 % of 128 patients with myocardial infarction failed to show definite electrocardiographic signs of this 1/2 year or more later The majority of them, however, belonged to group 2 who also in the acute stage had non diagnostic ECG

Electrocardiographic regression appeared to be somewhat more frequent in posterior infarctions than in anterior infarctions, possibly because the posterior location is less accessible to electrocardiographic exploration Also inaccessibility of infarction to the usual electrocardiographic leads probably accounts for a number of the non diagnostic ECGs in patients belonging to group 2

In the patients from group 1 with persisting diagnostic sign of infarction, the mean SGOT value in the acute stage was 172 units Corresponding SGOT values for the remaining patients of group 1 and for patients in group 2, were 145 and 102 units respectively This indicates that electrocardiographic regression is most likely to occur in patients with relatively small infarctions

There could not be demonstrated any relation between regression in ECG and the patient s age at infarction or between regression and relative heart volume estimated roentgenologically immediately following the acute stage

The diagnosis of previous posterior infarction could be made by leads II + III in 26 out of 41 patients In 13

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cases lead aVF provided confirmatory evidence and in 2 cases the necessary evidence for the diagnosis. In all the 47 cases with persisting signs of anterior infarction, the diagnosis could be made by the precordial leads. Definite diagnostic signs were found in lead I in only 5 cases, and in leads I + aVL in only 10 of these patients. Signs of infarction were absent from lead V_4 in 15 of the 47 patients with previous anterior infarction, but 2 of them had diagnostic signs in extremity leads. If only the three standard extremity leads (I, II and III) and one precordial unipolar lead, e. g. V_4, had been employed, evidence of previous anterior infarction would have been missed in 13 (28 %) out of 47 cases, and there would have been doubt about the diagnosis of previous posterior infarction in 15 (37 %) out of 41 cases.

Summary

One hundred and twenty eight patients were examined with a 12-lead electrocardiogram 1/2—2 years following acute myocardial infarction. Originally 105 had unequivocal electrocardiographic evidence of infarction. The remaining 23 patients had non-diagnostic electrocardiograms in the acute stage, but the diagnosis was confirmed by increased SGOT activity and other laboratory evidence. In the former group the electrocardiogram no longer showed definite signs of infarction in 17 cases (16 %), but in no case had the electrocardiogram reverted to normal. Among the 23 patients with non-diagnostic electrocardiograms in the acute stage there were still none with unequivocal evidence of infarction, and in 3 cases the electrocardiogram had become normal. In all, 40 (31 %) out of 128 patients failed to show definite electrocardiographic signs of previous myocardial infarction.

The regressive changes apparently took place within the first 1/2—1 year after infarction. The group of patients who lacked diagnostic electrocardiograms of previous infarction had lower SGOT-values in the acute stage than the other patients, indicating that they may have had smaller infarctions.

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Leukocytosis During Corticosteroid Therapy

By

G Biorck, L E Bottiger and E Orinius

Corticosteroid treatment of patients with various diseases is getting more and more common and the need to protect these patients from untoward side effects of the steroids is imperative On several occasions we have been puzzled by a pronounced leukocytosis occurring during treatment with prednisolone Could the leukocytosis be caused by an undiagnosed infection or could it be produced by the steroids themselves?

Materials and methods

Eleven hospitalized patients (4 men and 7 women aged 22—84 without fever signs of infection or haematological disorders were given peroral prednisolone 10 mg $\times$ 3 for 5—8 days White blood cells were counted every or every second day before during and after the treatment Mean values for the pretreatment period were calculated and subsequent values as average percentage increase From the differential counts a total average of granulocytes and lymphocytes were also calculated for the different periods

Results

The results are presented in fig 1 and table I It is evident that there is a rapid and considerable increase in the WBC values with a maximum on day 5—8, amounting to approximately 100 per cent This increase is found not only for granulocytes but — although to a lesser degree — for lymphocytes also

Discussion

It was demonstrated for ACTH (5) and for cortisone (3 6) that the administration of these substances was followed by leukocytosis but these observations seem to have attracted little attention

Available data support the assumption that the leukocytosis is due to a release from the marrow storage pool of mature cells (7) Such a release of mature cells is probably also the cause of the slight increase in the number of circulating lymphocytes observed by Finch et al and found in this study, a finding in contrast with the well known depressive effect on lymphoid tissue

It has been pointed out that the administration of steroids to patients with myelocytic leukaemia may be harmful and result in an acceleration of haematological deterioration (1, 2 5) This could imply that the steroid effect on the bone

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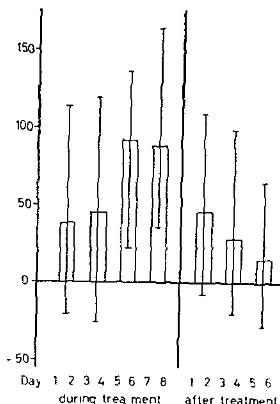


Fig 1 Average percentage increase in the number of circulating white blood cells during and after corticosteroid therapy

marrow is more profound than affecting a simple release of mature cells The studies of leukokinetics, now being performed in several centres, will probably give us better information on these problems

This short time study cannot answer the question how long steroid induced leukocytosis will persist The purpose of this experiment and communication is solely to draw attention to the clinically important steroid induced leukocytosis, the knowledge of which may be of great value for differential diagnosis during steroid therapy

Table I Results of differential counts, showing increase also in the number of lymphocytes

Treatment	No of differential counts	Segmented neutrophils	Lymphocytes
		Mean of absolute nos	
Before	29	3 200	2 000
During	26	5 400	3 000
After	18	3,800	2 400

Summary

Prednisolone in ordinary dosage (30 mg daily) increases the total number of circulating white blood cells as much as 100 per cent

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The A V Vishnevsky Institute of Surgery, Moscow, U S S R

Principles of Diagnostic Machine Construction[1]

By

A A Vishnevsky, I I Artobolevsky and M L Bykhovsky

There is no doubt that further progress in medicine is inseparable from the latest achievements in such exact sciences as chemistry physics mathematics and particularly cybernetics

The branch of cybernetics dealing with the use of electronic computers in clinical medicine is in our opinion not only of theoretical interest, but also of great practical importance

In our field computers can be used in two directions The first entails the employment of mathematical machine methods for processing broad medical information which in the long run leads to rapid and precise diagnosis The second application is the use of electronic computers for a thorough study of the various functional systems of the body

As representatives of clinical medicine we are first and foremost *interested* in the employment of machines for diagnosing diseases — which is the subject of our paper

Some clinicians believe that our desire to connect cybernetics and clinical medicine is a kind of bending to fashion This however, is not so In our paper we should like to lay particular emphasis on and substantiate the inherent inseparable connection existing between these two *scientific trends*, i e the youngest and the oldest one

Modern medicine has designed a great number of diverse instruments often very *fine* and ingenious which make it possible to carry out the most varied investigations on the patient And here we are *confronted* with a peculiar paradox the wider the information on the patient s condition, the *more difficult* it is for the doctor to *inter relate* all these data and to derive a general idea of the disease diagnosis Indeed, if the patient s condition is *characterised* by *many dozens* of signs, as is usually the case with modern methods of research, no doctor is able to assess all these numerous *symptoms* in their totality, in fact, *he is* at times not even in a position to comprehend them

This may be illustrated by an example For a proper pre-operative diagnosis of a

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[1] Lecture given at Serafimerlasarettet Stockholm Nov 18 1963

TABLE I Congenital heart diseases

Symptoms ↓→S_i	Cyanosis 1 01	Early cyanosis 1 02	Late cyanosis 1 03	*Left ventricular* hypertrophy 5 24	Prominent pulmonary artery 5 25	Atriovasal angle visible in second oblique position 5 26	Atrio vasal angle displaced upwards 5 27	Enlarged pulmonary artery as compared to aorta 5 28	Large pulse amplitude in the ascending aorta 5 29	Notes
B_j	Patent ductus arteriosus *without pulmonary hypertension*									
1 01	0 05	0 00	1 00	0 15	0 05	0 85	0 50	0 75	0 25	4 31, 6 23, 8 10, 8 25
	Patent ductus arteriosus with pulmonary hypertension									
1 02	0 05	0 00	1 00	0 05	0 05	0 85	0 75	1 00	0 25	4 31 7 09, 8 11, 8 26
	Atrial septal defect + patent ductus arteriosus									
1 18	0 05	0 10	0 90	0 10	0 06	0 85	0 75	1 00	0 25	—
	Ventricular septal defect + patent ductus arteriosus									
1 19	0 05	0 00	1 00	0 25	0 05	0 85	0 75	1 00	0 25	—
	Patent ductus arteriosus with reversed shunt									
2 01	0 75	0 00	1 00	0 05	0 05	0 85	1 00	0 60	0 10	4 39, 7 09 8 11, 7 05
	Aorto pulmonary window with reversed shunt									
2 02	0 75	0 00	1 00	0 05	0 05	0 85	1 00	0 60	0 00	—
	Ventricular septal defect with reversed shunt									
2 03	0 75	0 10	0 90	0 05	0 10	0 85	1 00	0 60	0 00	4 42 7 08 8 11 8 26 7 05

child with a congenital heart disease, it is necessary to make dozens of complex and even dangerous investigations They include electrocardiography, phonography, ballistocardiography, electrokymography, contrast roentgenological investigation of the heart cavities, aortography, probing of the heart cavities and so on To assess all this broad information is not easy

It is, of course, constantly necessary to devise new, improved and refined methods of investigating the human body All this, however, will be of little value unless we are able to cope with the mass of information supplied

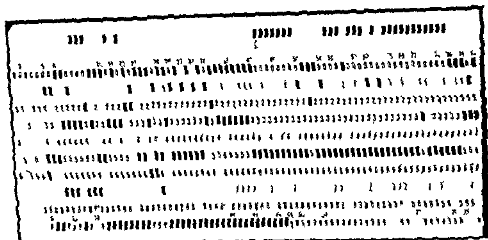


Fig 1

by the new methods of research Elaboration of cybernetic systems of diagnostic thinking and assessment of the extensive information supplied by them is a task of first priority

In the Cybernetics Laboratory of the A V Vishnevsky Institute of Surgery we have on the basis of the Ural 2 electronic computer designed a diagnostic system which we first used experimentally for diagnosing congenital heart diseases

The internal organisation of our diagnostic system can as it were be divided into two parts on the one hand there a medical memory i e accumulated medical experience in a given field of disease on the other hand there is a logical process of thinking which makes it possible to compare the symptoms obtained on examining the patient with our medical experience

Let us begin with the system's medical memory It is a special table which can be drawn up for any class of ailments As an example we give a table for congenital heart diseases (table I) Numbered vertically are altogether 200 symptoms encountered in congenital heart diseases while horizontally are the names of the 50 most widespread heart anomalies amenable to surgical correction

In this table symptoms that are always encountered in a given disease are denoted as unity while symptoms which are never encountered are designated as zero All the other squares of the table are filled with fractional numbers showing the frequency of a given symptom in each one of the heart diseases Besides in the Notes column we see groups of symptoms or syndromes which fully describe the given disease i e if the set of symptoms thus singled out is found in the patient he is affected with a corresponding heart disease

Such a table represents concentrated medical experience or medical memory in the given class of ailments For

TABLE I Congenital heart diseases

Symptoms ↓→S	Cyanosis 1 01	Early cyanosis 1 02	Late cyanosis 1 03	Left ventricular hypertrophy 5 24	Prominent pulmonary artery 5 25	Atriovasal angle visible in second oblique position 5 26	Atriovasal angle displaced upwards 5 27	Enlarged pulmonary artery as compared to aorta 5 28	Large pulse amplitude in the ascending aorta 5 29	Notes
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1 18	0 05	0 10	0 90	0 10	0 06	0 85	0 75	1 00	0 25	–
	Ventricular septal defect + patent ductus arteriosus									
1 19	0 05	0 00	1 00	0 25	0 05	0 85	0 75	1 00	0 25	–
	Patent ductus arteriosus with reversed shunt									
2 01	*0 75*	*0 00*	*1 00*	*0 05*	*0 05*	*0 85*	*1 00*	*0 60*	*0 10*	*4 39 7 09 8 11 7 05*
	Aorto pulmonary window with reversed shunt									
2 02	0 75	0 00	1 00	0 05	0 05	0 85	1 00	0 60	0 00	
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child with a congenital heart disease it is necessary to make dozens of complex and even dangerous investigations They include electrocardiography phonography, ballistocardiography electrokymography contrast roentgenological investigation of the heart cavities aortography probing of the heart cavities and so on To assess all this broad information is not easy

It is of course constantly necessary to devise new improved and refined methods of investigating the human body All this however will be of little value unless we are able to cope with the mass of information supplied

F g 3

t s tl e e methods of research Elabora n of c bernet c sy tem of diagnostic tl k ng and a sessment of the extensive I mat o ppl ed by them is a task f t p or y

I I e C bler et s Lal oratory of the \ \ \ l es ky In t tute of Surgery we h e tl e ba of the Ural 2 l r mp ter de g ed a diag em which we first used ex l e tall f d agi os ng congen tal l l e r e

I l e er al a a on of our f em a a t were be l le l pa n he one l and a e l memor e a c l r l al exper ence n a d l d c e he o her hand l al p e l th k ng l k l l le mpare the l l r l ex m ng the l l n e l l exper ence I l l r em s med al l pe al al le wl cl can l l t la of a lments

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Such a table represents concentrated med cal experience or medical memory in the given class of ailments For

instance, the table for the congenital heart diseases we are interested in contains 10,000 squares with numbers

Where did we take these numbers from, determining the probability of this or that symptom in the given disease?

We obtained them by processing our extensive medical archives containing several thousand medical histories Each one of these histories was processed by a physician and presented in the form of a punched card with all the symptoms found in the patient punched on it (fig 1)

Using these cards, we calculated the probability of each symptom in all the congenital heart diseases chosen by us This enormous work was carried out in a relatively short period of time with the aid of an automated medical information machine designed by us on the basis of a tabulator

The logical diagnostic process proper, effected by the machine, consists of two parts a) determinist logic and b) probability logic in conjunction with logic based on the phase internal principle

The diagnostic process begins with determinist logic To begin with, the punched card with the symptoms found in a given patient on it is introduced into the computing machine, with the medical table already put into its electronic storage In the machine are first compared the data of the punched card with the set of symptoms shown in the "Notes" column of our memory table If the symptoms found in the patient coincide with one of the pathognomonic complexes the machine puts out as a diagnosis the appropriate disease name shown in the table

If the symptoms of the patient coincide with none of the complexes shown in the "Notes" column, they are compared with all the determined symptoms denoted in the table by zeroes and unities

The machine makes these comparisons with all the 200 symptoms, rejecting the ailments which are impossible in a patient with a given clinical picture In other words, we are carrying out an extensive system of differential diagnosis, which is beyond the powers of any doctor confronted with so many symp toms

After all this we shall have a small number of ailments (say, five or six types of congenital heart disease) which are possible for a given clinical picture That is where the stage of determinist logic ends and the second stage begins, a stage intended to find out with which of these 5—6 diseases the patient is really affected For this purpose the ailments left after the application of determinist logic are assessed by means of probability logic

The second stage, that of probability logic, consists in calculating the probabilities of the remaining diseases by means of complex mathematical transformations performed by the machine In view of the fact that these transformations, expressed in complex mathematical formulas, are of interest to experts alone, allow me not to touch on them here The purpose of these transformations in brief outline is to determine the information measure or, in other words, the relative 'weight' of each symptom

in a given disease The importance of this factor depends on a) the incidence of the symptom in a given heart disease, b) its incidence in the remaining heart diseases, and c) the relative frequency of heart diseases as such

To explain why the concept 'the diagnostic weight of the symptom was introduced', I shall cite the following example the finding of some sign, say, No 1 in 90 per cent of the patients affected with disease A does not itself render it of diagnostic value This value will be great if in ailments B C D and others this sign is encountered much more rarely but will be insignificant if in these cases it is encountered just as frequently On the other hand the diagnostic value of a rare symptom may be great if it is encountered only in one ailment

Taking into account these weight values of symptoms and the frequency of each of the congenital heart diseases thus singled out the machine calculates the probability of ailments possible for a given patient The numbers obtained are compared with some criteria i e threshold calculated approximately for each ailment If this threshold has been reached for some disease it will be the diagnosis of this disease If not another investigation has to be made for the group of more serious ailments which will provide additional information Then the above cycle is repeated

Parallel with probability logic we used in our diagnostic system logic based on the phase interval principle The introduction of this logic serves to increase the reliability of a diagnostic assessment made by means of probability logic

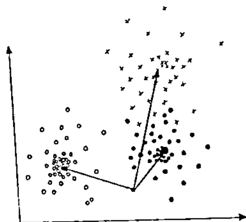


Fig 2

In order to explain this part of the second logical process we should like to give some geometrical illustration Suppose we have to try to show the patient's condition on a graph To simplify the case let us assume that the ailment is described by two symptoms only Then by plotting the value of one sign on the X axis and that of the other sign on the Y axis we shall obtain a point on the plane, describing the condition of a given patient (fig 2) Let us suppose further that on this plane we have to show, by means of points, the condition of all the patients suffering from a given disease Naturally not all the patients will be characterised by the same point for one and the same ailment has different symptoms in different people Thus an area would be formed by a group of points Similarly if we were to describe by points the condition of those patients who are affected with other diseases, we would obtain another area i e , a group of points situated at some distance from the first area In

instance, the table for the congenital heart diseases we are interested in contains 10,000 squares with numbers

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2 Creation, on the basis of diagnostic machines, of a system for automatic assessment of information on and control over the body's vital functions during an operation This applies to automatic regulation of the arterial pressure level, automatic anaesthesia, automatic control of an artificial circulation apparatus, an artificial kidney, etc

3 Development of a diagnostic system into which it will be possible to introduce not only data on the current condition of the patient, but also the basic data relating to his life history so as to be able to treat the patient and not the disease to a much greater extent than is possible today

4 Elaboration of a single detailed form of medical history applicable to every type of disease, so that on the basis of an automatic information system one can not only make use of the experience of one s own clinic, but also exchange experience within the framework of all the clinics of the country and between countries

In describing the prospects of cybernetics in medicine, we hold it necessary to emphasise that cybernetics by no means aims to replace the physician by some supranatural machine but is intended to put into his hands a tool which will substantially increase his logical and creative possibilities in the struggle for man s health

mathematics such areas are called phase areas Now let us consider a new patient for whom we are going to make a diagnosis Let his condition be represented on the plane by some new point, then the purpose of the diagnostic process considered is to find out to which of the previous areas this point, representing the symptoms of the given patient, is closer With this end in view we have to find what is called phase intervals, i e the distance between the given point and one area or another The patient is believed to be affected with the disease whose area is at the shortest distance from the given point

In describing phase-interval logic we cited a very simple example of diagnosing among three diseases with two symptoms However, our diagnostic system for congenital heart diseases provides for 50 ailments with 200 symptoms Accordingly, in geometrical space 50 phase areas are designated and symptoms are plotted not in one but in many planes, the number of which depends on that of symptoms

Thus, in this logic the idea of multidimensional space is used For many of us who are accustomed to three-dimensional life, if I may say so, this idea is difficult to conceive

The above mentioned principles of diagnostic system construction were first realised in the Cybernetics Laboratory of our Institute about two years ago Its first experimental operation in the field of congenital heart diseases has shown very promising results Some 200 diagnoses were made In approximately 90—95 per cent of the patients the diagnosis was correct (for various diseases the diagnosis differs in the accuracy)

In some cases the system showed no diagnosis, instead it assessed the probability of a disease For instance, in patient M the probability of an aorto pulmonary fistula was equal to 70 per cent In the course of this work we had more than once to correct the mistakes of the system's medical memory, and we shall perhaps have to do this again and again in the future Curiously enough, however, there were cases when a hypothesis put out by the machine did not coincide with that put forward by physicians, while the operation confirmed the "machine" diagnosis

In conclusion, we should note the universality of our diagnostic system Transition from one type of ailment to another is effected by appropriate changing of the medical memory tape For instance, we are now completing work on medical material for differential diagnosing of mechanical jaundices Moreover, such a system can be used not only for solving general problems of diagnosis, but also for performing particular diagnostic processes, for instance, electrocardiographic diagnosis, roentgenovasographic diagnosis, etc

Now a few words about the future prospects of the trend under discussion The most important of them are as follows

1 Development of a more extensive diagnostic system, i e a system which can be used in diagnosing other important forms of disease, and creation of a general system in the form of a ramified arrangement of particular diagnostic systems

Acta Medica Scandinavica Vol 176, fasc 2, 1964

Recherches sur l'evolution preclinique du myelome multiple

par

OLAF NORGAARD

Dans la troisieme partie de notre travail « Recherches sur des serums humains fortement anticomplementaires » achevé en 1951 mais remis à l impression deux ans plus tard et publié en 1954 nous avons mentionné les résultats des examens électrophorétiques de 24 serums fortement anticomplementaires Parmi ces serums 21 présentaient sur leur diagramme un pic γ pointu et éleve le constituant M sur ces 21 malades 3 seulement présentaient des signes de myelome multiple En 1951 un tel diagramme électrophorétique n avait été constaté que chez des malades atteints de myélome multiple (et dans un nombre très restreint de cas de malades de Waldenstrom) nous avons donc suppose que les malades dont l unique symptome etait la présence du constituant M dans le sérum pouvaient se trouver à la phase initiale d un myélome multiple Effectivement des symptomes de myelome multiple ont apparu ultérieurement chez 4 des malades examines en 1951 et chez un malade examiné en 1953 Nous rapportons les observations de ces 5 malades qui montrent que le myelome multiple a une évolution pre clinique très longue Quelques unes des observations des autres malades figurent dans une publication faite en 1957 , les autres seront publiees ultérieurement

Materiel et méthodes

Les examens électrophorétiques du sérum ont été pratiqués selon la même méthode que celle employée antérieurement Elle a été minutieusement décrite par Marner en 1955 (4) Les renseignements contenus dans les observations ont été obtenus par l étude des dossiers des services dans lesquels les malades ont été admis Dans beaucoup de cas les médecins de ces services ont fait pratiquer les examens sur notre demande Les 5 malades étudiés ici ont été mentionnés brièvement par Norgaard en 1954 et 1955 (6) les numéros des observations sont les memes que ceux employés dans ces publications

Examens électrophoretiques

Les résultats des examens électrophorétiques figurent sur le tableau I On voit que dans tous les sérums il y a une augmentation rela

Ce travail est parvenu à la rédaction le 17 Décembre 1963

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Materiel et methodes

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Examens electrophoretiques

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Ce travail est parvenu a la redaction le 17 Décembre 1963

73 1950

73 1961

79 1950

79 1956

97 1952

97 1956

97 1960

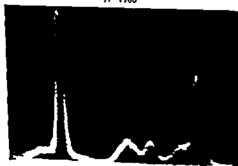


Fig. 1. Diagrammes d'électrophorèse des sérums 73, 79 et 97. Les diagrammes des sérums No 55 et No 66 sont du même type.

TABLEAU I Examens electrophoretiques Moment des examens concentrations relatives et protéine totale Les valeurs normales dans la premiere ligne ont ete crees du travail de Marner (4)

No	Annee	Albumine	α_1- Globuline	α_2-	β-	γ-	Protéine totale
(Normal)		57 6	3 8	7 5	15 1	16 1	—
55	1950	28 9	6 9	16 5	8 6	39 3	8 8
66	1950	46 8	3 5	8 1	12 7	29 0	8 8
73	1950	43 2	5 2	9 4	14 5	28 0	7 6
73	1961	42 6	5 1	7 7	10 4	34 2	8 0
79	1950	41 5	5 1	7 8	13 0	32 7	—
79	1956	38 4	2 8	6 3	13 7	38 8	8 0
97	1952	43 3	7 9	8 4	14 7	25 7	7 0
97	1956	50 5	4 6	4 8	14 9	25 2	7 0
97	1960	32 2	7 3	9 2	11 2	40 1	9 1

tive du pourcentage de la globuline γ et une diminution relative du pourcentage de l'albumine Dans les cas ou plusieurs examens ont été pratiqués chez le meme malade, ces deux perturbations sont plus marquées lors du dernier examen Quelques diagrammes sont représentes sur la fig 1 on constate régulierement un pic γ pointu et elevé et on observe que lorsque plusieurs examens ont été effectués chez le même malade a plusieurs années d intervalle, le type du diagramme demeure inchange Les diagrammes des autres sérums etaient du même type que ceux representes ici

Il a été pratiqué un examen immuno-électrophorétique des sérums n 73 et 97 Dans les deux cas la conclusion était Myélome γ

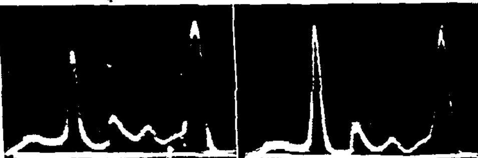
Observations

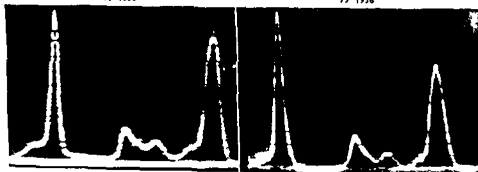
N° *55* Femme, née en 1900 Sérum fortement anticomplémentaire depuis 1950 Admise au mois de Mai 1950 a l'Hopital departemental de Tonder pour cholécystite A cause de la constatation d une electrophorese anormale, examinée pour myélome multiple Radiographie du crane, cotes coeur poumons, bassin pas de signe de myelome multiple Urine —proteine, hgb 68—98, V S 20 Ponction sternale 17 % de plasmocytes, tous normaux

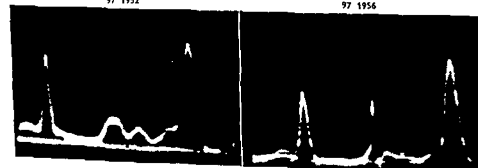
Admise a nouveau a l Hopital departemental de Tonder, en Févrrier 1961 pour kyste de l ovaire droit Examinée de nouveau pour myélome multiple Elle n avait pas présente de symptomes cliniques de cette affection

Radiographie au niveau de la 5e cote droite, lateralement en arriere, on note un processus de destruction osseuse La cote de trame irréguliere est élargie en forme de fuseau sur un trajet d'environ 3 cm Une lacune de grandeur d une graine de fève environ, est visible au niveau de la clavicule droite Au niveau du crane il semble y avoir une lacune de la taille d un pois dans la région temporale droite Absence de proteine dans l urine a plusieurs examens V S 30-16-15-15 Ponction sternale 16 % de plasmocytes tous normaux

Admise a nouveau au mois de Mars 1963 a l Hopital departemental de Tonder pour « hernie ventral » Radiographie du rachis lombaire et du bassin halistéresie et microgeodes bien limitées arrondis de la taille d un grumeau, dans la structure osseuse Urine — protéine — protéine de Bence Jones V S 39—26, hgb 124 g/l, globules rouges 3,73 millions globules blancs 5,240







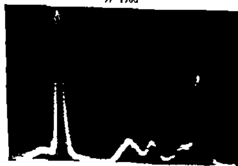


Fig. 1. Diagrammes d'électrophorese des sérums 73, 79 et 97. Les diagrammes des sérums No 55 et No 66 sont du même type

TABLEAU II Symptomes cliniques examens sanguins, urinaires radiologiques de 5 malades, chez lesquels un pouvoir anticomplémentaire intense et de la protéine M dans le sérum ont apparu de 6 à 17 ans avant l apparition de symptomes cliniques

No 55	No 66	No 73	No 79	No 97
1950 Pouvoir anticomplémentaire intense protéine totale 8 8, dont 39 3 % protéine M, V S 20, Hgb 68—98, urine — prot, radiogr rien d anormal, ponction stern 17 % de cellules plasm normales *1961* V S 30—16—15, ponction stern 16 % de cellules plasm normales Radiogr lacunes dans plusieurs os, urine — prot *1963* Hgb 12 4 g% V S 39—26 urine — alb, radiogr plusieurs lacunes dans les os urine — prot — Bence Jones	*1945* Pouvoir anticomplémentaire intense Hgb 95 V S 28 urine—prot *1950* Protéine totale 8 8, dont 29 %, protéine M *1961* Hgb 81, V S 57—65—78—71—71 Ponction stern 4 25 % de cellules plasm anomales Radiogr thorax rien d anormal Urine — alb — Bence Jones, electrophorese sur papier 42 % de globuline γ *1962* Douleurs au niveau du dos Radiogr écrasement de plusieurs vertebres V S 92—83 urine — alb — Bence Jones	*1950* Pouvoir anticomplementaire intense protéine totale 7 6 dont 28 % protéine M, Hgb 97—99 V S 53—50—26, urine — prot *1958* Hgb 95 V S 39, urine — alb *Jan 1962* Hgb 66 V S 127—105 Ponction stern 21 % de cellules plasm anomales Radiogr rien d anormal Proteine totale 8 0 %, dont 34 2 % protéine M *Juillet 1962* Ponction stern 18 % de cellules plasm quelques unes legerement anomales *Aout 1963* Hgb 65 V S 130 Radiogr rien d anormal	*1949* Pouvoir anticomplementaire intense, protéine M 32 7 %, Hgb 98, V S 19—12 urine—alb, radiogr rien d anomal ponction stern rien d anormal *1955* Perte de poids 9 kgs Hgb 88, V S 21—17, urine — alb, ponction stern 14 % de cellules plasm anomales Urine — alb protéine totale 8 %, dont 38 8 % protéine M Mort 19/4 1956 Pas d autopsie	*1952* Pouvoir anticomplémentaire intense, protéine totale 7 0, dont 25 7 % proteine M Hgb 119—99, V S 7, urine—alb radiogr rien d anormal *1954* Hgb 100 *1959* Hgb 97, V S 9 *1960* Protéine totale 9 1 %, dont 40 1 % protéine M V S 50 ponction stern 5 5 % de cellules plasm normales urine — alb radiogr rien d anormal *1962* Hgb 9 8 g% V S 60 douleurs aux os Radiogr lacunes écrasement de plusieurs vertebres ponction stern 16 % de cellules plasmatiques anomales

Au mois d Aout 1963 le médecin fait savoir que l état général est parfait et surtout qu il n y a pas de symptomes de myélome multiple

N 66 Femme née en 1898 Sérum fortement anticomplémentaire depuis 1945 Admise au mois de Mai—Juin 1945 au service de chirurgie de l Hopital départemental de Kolding avec le diagnostic de maladie de Basedow Guérison apres administration d iode et strumectomie V S 28 hgb 95 urine — protéine En 1960 on constate une glycosurie qui s agrave rapidement et c est la raison pour laquelle on a fait admettre la malade au service des maladies internes de l Hopital Départemental de Kolding On porte le diagnostic de diabete sucré et on constate qu il n y avait pas de symptomes d autres affections V S 57 65 78 71 71 A cause de cette accélération de sédimentation on pratique une ponction sternale Sur le myélogramme on trouve 4 25 °₀ de plasmoblastes atypiques cellules de myélome

Radiographie du thorax rien d anormal Hgb 81 globules rouges 3 89 millions globules blancs 6 000 Formule leucocytaire neutrophiles en baton 8 °₀ neutrophiles segm 41 °₀ lymphocytes 44 °₀ monocytes 7 °₀ Protidémie totale du sérum 7 3 °₀ électrophorèse sur papier albumine 35 5 °₀ globuline alpha 11 6 °₀ globuline beta 9 8 °₀ globuline gamma 42 °₀ Urine — protéine — Bence Jones

Dans l été de 1962 elle présente une dorsalgie apres un effort exagéré Admise à nouveau au mois de Mai—Juin 1962 La radiographie du rachis montre maintenant distinctement un écrasement de la 1ère vertèbre lombaire et de la 11ème vertebre dorsale La trame osseuse de toutes les vertebres dessine de larges mailles Il semble y avoir des destructions au niveau de la 12ème vertèbre dorsale et probablement aussi dans les 3ème et 4ème vertèbres lombaires V S 92—83 urine — protéine — protéine de Bence Jones Radiothérapie pendant le séjour de la malade a l Hôpital Elle est toujours en vie au mois d Août 1963

N 73 Homme, né en 1889, sérum fortement anticomplémentaire depuis 1950 Il est admis au mois de Janvier Février 1950 au service des maladies internes à l Hôpital Central de Randers Diagnostic pneumonie, Hgb 97—99 V S 53—50

Admis à nouveau au meme Hôpital en 1958 Diagnostic bronchite chronique emphysème pulmonaire, séquelles de phlébite crurale droite Hgb 95 °₀ globules rouges 4 43 millions valeur glob 0 87, globules blancs 4 680 Numération différentielle neutrophiles segm 52 °₀ éosinophiles 7 °₀ lymphocytes 37 °₀ monocytes 3 °₀ myélocytes 1 °₀ plaquettes 152 000 V S 39 urine — protéine

Admis à nouveau au mois de Janvier—Février 1962 pour examen a cause de la constatation d une électrophorese anormale A l admission on n a rien trouvè d anormal abstraction faite d une tuméfaction de l hypochondre gauche Par une urographie directe on constate qu il s agit probablement d une tumeur rénale Hgb 66 globules rouges 3 45 millions valeur globulaire 0 87 globules blancs 3 960 Formule leucocytaire neutrophiles en batons 2 °₀ neutrophiles segm 58 °₀ éosinophiles 3 °₀ lymphocytes 25 °₀ monocytes 12 °₀ Plaquettes 158 000 V S 127—105 Urine — protéine quelquefois pourtant (—) protéine Ponction sternale 21 °₀ de cellules plasmocytaires décrites comme suit

« Il y a un nombre fortement augmenté de cellules plus ou moins semblables à des plasmocytes comprenant morphologiquement aussi bien des petites cellules de couleur foncée semblables a des lymphocytes que des cellules présentant les critères ordinaires des plasmocytes de même que des cellules plus gran des atypiques en partie nucléolées soit à type de leucoblaste soit de type réticulaire Conclusion myélome multiple probable mais possibilité aussi de maladie de Waldenstrom Radiographie de crane rachis bassin os creux longs pas de signe de myélome multiple

Le malade est transféré dans le service de chirurgie ou l on pratique l extirpation du rein gauche et de la tumeur de la capsule sur

rénale Diagnostic histologique Carcinome rénal (hypernephrome)

Réadmis au service de maladies internes au mois de Juillet Aout 1962 a cause d une thrombophlébite crurale droite Ponction sternale 18 % de plasmocytes Description « dans les frottis de moelle il a été trouvé un nombre fortement augmente de plasmocytes, peut etre même plus qu il n'en résulte de la numeration , car il y a plusieurs cellules a noyau nu et des cellules un peu traumatisées qui ne peuvent pas être identifiées Les plasmocytes sont relativement bien différenciés mais certains présentent toutes les transitions entre des cellules d aspect tout a fait normal et des cellules anormales un peu plus grandes de type reticulaire ou plus petites de type lymphocytaire

Conclusion myélome multiple probable

Apres l opération on a pratiqué de la radiotherapie S est présenté a plusieurs reprises aux examens de controle, la derniere fois au mois d Août 1963 L hémoglobine s est maintenue tout le temps aux environs de 65 Is V S aux environs de 130 Plusieurs examens radiographiques du systeme osseux n ont montre ni signes de myélome multiple, ni métastases

N 79 Homme ne en 1880 Sérum fortement anticomplémentaire depuis 1949 Admis au mois de Novembre—Decembre 1949 a l Hopital Départemental a Tonder Diagnostic cardiopathie (angine de poitrine myocardite dégénérative) Examiné sur la demande de l auteur aucun signe de myelome multiple Hgb 98 V S 19 urine — proteine Ponction sternale rien d anormal Radiographie de crane rachis bassin cotes articulation coxo femorale pas de signe de myélome multiple

Admis a nouveau au mois de Novembre—Décembre 1955 Diagnostic cardiopathie (dilatation cardiaque Cette derniere annee perte de poids de 9 Kgs il y a une dyspnée d effort qui s aggrave Objectivement rien d anormal Urine absence d albumine V S 21—17 hgb 88 globules rouges 4 01 millions valeur globulaire 1 10 globules blancs 4 760 Formule leucocytaire neutrophiles en baton 5 %, neutrophiles segmentés 30 %, éosinophiles 3 % lymphocytes 57 % monocytes 5 % Erythrocytes normaux Radiographie du systeme osseux pas de signe de myélome multiple Ponction sternale 14 % de plasmocytes « Plusieurs des cellules plasmatiques sont grandes avec des noyaux relativement grands souvent nucleoles Il s'agit de cellules plasmatiques atypiques du type qui se rencontre dans le myelome multiple D ailleurs on ne voit pas de cellules anormales » Diagnostic histologique moelle osseuse avec présence en quantite anormale de plasmocytes en partie atypiques probablement du myélome multiple Mort a domicile de 19 Avril 1956 de thrombose coronarienne Pas d autopsie

N 97 Homme né en 1900 Sérum fortement anticomplémentaire depuis 1952 En 1952 admis a l Hopital Saint Joseph et au service de neuro chirurgie Rigshospitalet pour sténose du col vésical et hématome sous dural Hgb 119—99, V S 7 radiographies crane rachis bassin membres superieurs et inferieurs rien d anormal De 1953 a 1959 admis a plusieurs reprises au service de chirurgie D Hopital de Bispebjerg pour hypertrophie de la prostate sténose du col vesical En 1954 Hgb 100 globules rouges 5 millions valeur globulaire 1 0 globules blancs 3 700 Formule leucocytaire neutrophiles segmentés 38 % neutrophiles en baton 2 % éosinophiles 6 % monocytes 17 % grands lymphocytes 18 % petits lymphocytes 19 %

En 1959 Hgb 97 V S 9 En 1960 et 1962 admis au service de maladies internes B de l Hopital de Bispebjerg Diagnostic myelome multiple En 1960 Hgb 86—74 globules rouges 3 8 millions Valeur globulaire 0 95 V S 100—50 Radiographies crane rachis bassin rien d anormal Urine — alb Ponction sternale 5 5 % de plasmocytes tous normaux

Au printemps de 1962 douleurs dans la région lombaire Radiographie écrasement de la premiere vertebre lombaire ultérieurement aussi des 11eme et 12eme vertebres dorsales V S 60 Hgb 9 8 g % Ponction

sternale 16 % de plasmocytes nombreuses formes anormales Diagnostic histologique myélome multiple En 1963 radiographie lacune au niveau de la 6eme cote droite

Constatations biologiques et radiologiques au cours de la période preclinique

Les 5 malades présentent un myelome multiple mais chez le N° 55 et le N° 73 il n y a pas de symptomes cliniques chez le N° 66 et le N° 97 il y a des symptomes cliniques certains (douleurs osseuses, fractures spontanees) chez le N° 79 il y a des symptomes cliniques douteux (amaigrissement de 9 Kgs) Chez les 5 malades le premier symptome est un pouvoir anticomplementaire intense et la présence de protéine M dans le sérum Quand ce symptome apparait pour la première fois l hemoglobine et la V S sont normales (chez le N° 73 il y a cependant constamment une V S legèrement augmentée) L evolution des symptomes semble avoir lieu dans l ordre suivant

1 — protéine M et pouvoir anticomplementaire intense,

2 — anemie augmentation des plasmocytes dans la moelle osseuse,

3° — symptomes cliniques et alterations radiologiques osseuses

Cet ordre n est pourtant pas constant, car chez le malade N 55 on trouve une augmentation des plasmocytes et des altérations radiologiques osseuses à une époque ou il n y a pas de symptomes cliniques

La période préclinique c est à-dire la période ou il y a un pouvoir anticomplémentaire considerable et de la protéine M dans le sérum eventuellement un nombre augmenté de plasmocytes dans la moelle osseuse et de l anémie, mais pas de symptomes cliniques, dure 6 ans chez le N° 79, 17 ans chez le N° 66, 10 ans chez le N° 97 et 13 ans chez le N° 55 et le N° 73 Chez les deux derniers malades il n'est pourtant pas encore apparu de symptomes cliniques , il est donc possible que dans ces cas la la période preclinique devienne encore plus longue Malgre les troubles proteiques serieux dans le serum, on note durant cette periode un bien etre parfait, seulement le N° 73 présente une bronchite permanente Il est bien connu que des malades presentant un myelome multiple ont une resistance très diminuee aux infections Cette resistance diminuee n'existe donc pas dans la periode preclinique, bien que les troubles proteiques soient les memes que dans le myélome multiple entièrement constitue

Dans le serum provenant du N 73 et du N° 79 on a observe — dans la période preclinique — une augmentation faible du pourcentage relatif de la globuline γ Dans le serum provenant du N° 97 la globuline γ ne presente aucune alteration de 1952 à 1956 , en 1960, c'est a-dire à l *époque ou* le myélome multiple s est manifeste le pourcentage relatif de globuline γ a augmenté considérablement Une augmentation semblable de la globuline γ lors du passage du myelome multiple de l etat latent a la phase ou il est cliniquement manifeste a ete décrite par Olhagen et Liljestrand en 1955 (7)

Publications anterieures

Le fait ques les troubles proteiques de serum dans le myélome multiple peu

vent apparaitre quelque temps avant les symptomes cliniques, a ete mentionne anterieurement dans quelques publications

En 1937 Prentis (9) rapporte le cas d'un malade chez lequel il a ete constate, lors des examens annuels de 1928 a 1935, de la proteine de Bence Jones dans l'urine Durant cette periode le malade etait parfaitement bien portant En 1935 on a constate une anemie grave, une V S legerement augmentee et un pouvoir anticomplementaire du serum, dans la reaction de B-W La radiographie des os a montre de la halisteresie diffuse Lorsque le malade est decede, peu de temps apres, on a etabli, par autopsie, le diagnostic de myelome multiple

En 1940 Gros et Brockmann (2) rapportent le cas d'un malade chez lequel de l'anemie et de l'hyperproteinemie ont ete constatees quelques mois avant les signes radiologiques Ils en tirent la conclusion que « die Hyperproteinämie lange Zeit den rontgenologischen Veranderungen im Skelettsystem vorausgehen kann »

Olhagen et Liljestrand (7) signalent en 1955 un malade chez lequel la premiere constatation avait ete l'existence d'alterations dans le diagramme d'electrophorese

date	albumine	globuline α	β	γ	proteines totales
14/I 1944	41 5	9 8	12 6	36 1	9 3
14/10 1944	43 1	7 4	13 6	35 9	9 1
28/5 1946	35 4	8 9	11 2	44 5	10 8

A tous les examens on a observe dans le diagramme electrophoretique un pic γ, etroit et eleve En 1944 il n'y avait pas de symptomes de myelome multiple, mais ce diagnostic a ete etabli en 1946 par radiographie et ponction sternale et confirme ulterieurement par autopsie L'evolution des troubles proteiques de serum d'abord des alterations constantes, puis une augmentation de la concentration de globuline γ et de la protidemie totale en meme temps qu'apparaissent des symptomes de myelome multiple, correspond exactement a ce qui a ete trouve chez le malade N° 97 mentionne dans le present travail

Dans la partie VII du travail « Recherches sur des serums humains fortement anticomplementaires » par Norgaard en 1957 (6) il a ete mentionne 3 cas surs et 2 cas probables de myelome multiple ou il a ete trouve de la proteine M dans le serum 2 ou 3 ans avant que le diagnostic de myelome multiple ait pu etre etabli

En 1958 Ossermann (8) mentionne un malade (case II) qui avait une V S fortement augmentee de 1948 a 1955 , au mois de Septembre 1955 il a ete trouve, par electrophorese, dans le serum « a characteristic homogenous spike », 35 % de cellules plasmocytaires anormales a la ponction sternale, mais pas d'alterations osseuses Au mois de Septembre 1956 la radiographie a revele des alterations osseuses Chez un autre malade (case III) l ordre des symptomes etait le meme La periode d'observation etait pourtant plus courte, Avril 1955 — Novembre 1957, et a cette derniere date il n'a pas pu être demontre d'alterations radiologiques

En 1958 Bloom et al (1) mentionnent un malade qui en 1937 et encore en 1949 presentait un serum fortement anticomplementaire A ces epoques là pas de

signes de myélome multiple, mais des symptomes cliniques de cette affection ont apparu en 1955

En 1959 Martin et Baker (5) ont publie l observation suivante femme agee de 43 ans presente au mois d Avril 1952 une protidemie totale de 11 2 dont 3 65 est de l albumine et 7 55 est de la globuline V S 117—131 Aux environs du jour de l an 1953 on constate une anemie isochrome V S 125 Dans la moelle osseuse sternale on trouve 13 % de cellules plasmocytaires toutes normales Radiographie du système osseux rien d anormal Des électrophorèses répetees de 1952 à 1957 ont montre un taux d albumine réduit et une globuline γ augmentee Au mois de Février 1957 la radiographie revele de l ostéoporose et de l écrasement de plusieurs vertèbres lombaires Dans l urine on trouve de la proteine de Bence Jones

En 1960 Waldenstrom (10) mentionne un malade qui depuis 1958 a presente une V S fortement augmentee et de la globuline γ augmentee dans le serum Par electrophorèse sur papier cette proteine se montre comme une bande etroite L examen des os ne montre pas de signe de myelome multiple mais il y a une augmentation régulière du nombre de cellules plasmocytaires dans la moelle osseuse L auteur considère comme probable que ce malade presente un myélome multiple

En 1961 Kanzow et al (3) mentionnent qu ils ont rencontre quelques malades accusant les alterations sériques caracteristiques de myelome multiple mais sans symptomes de cette maladie Chez quelques uns des malades des symptomes de myelome multiple se sont manifestes après quelques temps d observation chez d autres les symptomes cliniques manquent encore

Summary

In 5 patients a strongly anticomplementary power in serum and M proteinaemia are accidentally detected X ray examinations of the bones and other blood examinations are normal

After the lapse of 6 10 17 13 and 13 years respectively multiple myeloma is diagnosed in the 5 patients The symptoms have developed in the following sequence

1 M proteinaemia and strongly anticomplementary power 2 Anaemia and an increase in the plasmocyte count in the bone marrow and 3 Clinical symptoms and radiological changes in the bones

A similar development of the symptoms in the case of multiple myeloma has been previously described by 8 other authors in 1937—1961

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L auteur remercie Monsieur l Ingenieur civil A Birch Andersen et Monsieur le candidat en pharmacie Bendt Mansa (à l Institut Sérothérapique de l Etat Danois) qui ont executé les examens d electrophorese le dernier nommé a en outre executé l immuno-électrophorèse sur 2 des sérums mentionnés ici Je remercie également les medecins chefs des Hôpitaux mentionnés dans les observations de m avoir accordé la permission d emprunter les dossiers des malades

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The Ear Nose and Throat Clinic Lund and the Medical Clinic B (Renal Clinic)
Lund Sweden

Ototoxic Side Effects Following Treatment with Streptomycin, Dihydrostreptomycin, and Kanamycin

Connection with Dosage and Renal Function, Preventive Measures

By

PER ERLANSON and ANDERS LUNDGREN

Streptomycin dihydrostreptomycin kanamycin neomycin viomycin and vancomycin all of which are chemically similar antibiotic substances produced by the *Streptomyces* species have proved to be potentially ototoxic when administered parenterally The changes are probably located in the sensory cells of the inner ear (1) and affect either the organ of hearing or the organ of equilibration or both Neomycin is nephrotoxic as well the same is the case with viomycin and kanamycin although their effects in this respect are less severe (table 1) All are excreted by the kidneys

Streptomycin sulphate almost exclusively affects the organ of balance producing symptoms of dizziness and usually also bilateral reduction or disappearance of the caloric reaction The symptoms arise during treatment or at the latest within a week of withdrawal of the drug

According to a Report to the Council of Pharmacy and Chemistry (29 daily doses of 1 g 1 g and 0 5 g for 120 days caused dizziness in respectively 76 79 and 10 % of the cases Reduction or disappearance of the caloric reaction was noted in 64 32 and 22 % respectively

The risk of vestibular damage resulting from a daily dose of 1 g is slight, according to some investigators (24 33) Tompsett (33) considered that when calculated in mg per kg body weight the daily dose should not exceed 19 mg Graf (12) set the corresponding limit at 16 mg per kg body weight A daily dose of more than 24 mg/kg had produced disturbances of equilibrium in 86 % of his cases

Vogelsanger (34) was of opinion that the daily dose should not be higher than 1 g or 15 mg/kg and that a total dose of 10 g at the most does not often produce side effects According to Cawthorne and Ranger (3) such effects are unlikely when the daily dose does not exceed 0 5 g Like McDermott (2?) Vogelsanger (34) and others they emphasized the fact that impairment of the renal function increases the risk of damage

Dihydrostreptomycin sulphate even if given over only a short period and in small doses may cause damage to the hearing which often does not become manifest until about 1 to 6 months after the conclusion of treatment and which may lead to total deafness

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The Ear, Nose and Throat Clinic Lund and the Medical Clinic B (Renal Clinic)
Lund Sweden

Ototoxic Side Effects Following Treatment with Streptomycin, Dihydrostreptomycin, and Kanamycin

Connection with Dosage and Renal Function, Preventive Measures

By

PER ERLANSON and ANDERS LUNDGREN

Streptomycin dihydrostreptomycin kanamycin neomycin, viomycin and vancomycin all of which are chemically similar antibiotic substances produced by the *Streptomyces* species, have proved to be potentially ototoxic when administered parenterally The changes are probably located in the sensory cells of the inner ear (15) and affect either the organ of hearing or the organ of equilibration or both Neomycin is nephrotoxic as well the same is the case with viomycin and kanamycin although their effects in this respect are less severe (table 1) All are excreted by the kidneys

Streptomycin sulphate almost exclusively affects the organ of balance producing symptoms of dizziness and usually also bilateral reduction or disappearance of the caloric reaction The symptoms arise during treatment or at the latest within a week of withdrawal of the drug

According to a Report to the Council of Pharmacy and Chemistry (29) daily doses of 1 8—2 g 1 g and 0 5 g for 120 days caused dizziness in respectively 76 29 and 10 % of the cases Reduction or disappearance of the caloric reaction was noted in 64 32 and 22 % respectively

The risk of vestibular damage resulting from a daily dose of 1 g is slight according to some investigators (24 33) Tompsett (33) considered that when calculated in mg per kg body weight the daily dose should not exceed 19 mg Graf (12) set the corresponding limit at 16 mg per kg body weight A daily dose of more than 24 mg/kg had produced disturbances of equilibrium in 86 % of his cases

Vogelsanger (34) was of opinion that the daily dose should not be higher than 1 g or 15 mg/kg and that a total dose of 10 g at the most does not often produce side effects According to Cawthorne and Ranger (3) such effects are unlikely when the daily dose does not exceed 0 5 g Like McDermott (22) Vogelsanger (34) and others they emphasized the fact that impairment of the renal function increases the risk of damage

Dihydrostreptomycin sulphate even if given over only a short period and in small doses may cause damage to the hearing which often does not become manifest until about 1 to 6 months after the conclusion of treatment and which may lead to total deafness

Submitted for publication November 27, 1963

TABLE I Main forms of damage caused by ototoxic antibiotics

Antibiotic	Impairment of Balance	Impairment of Hearing	Kidney function
Streptomycin	+++	+	–
Dihydro streptomycin	+	+++	–
Neomycin	+	+++	+++
Viomycin	+	++	+
Vancomycin	–	+++	–
Kanamycin	+	+++	+

+++ = Damage common, ++ = Damage fairly common, + = Damage rare, – = No damage

(14, 31, 34, a o) Hamberger and Lidén (14) therefore issued a warning against the practice of giving daily treatment with dihydrostreptomycin for a longer period than one week Shambaugh et al (31) doubted whether dihydrostreptomycin should be used et all

According to Aschan s (1) experience, no side effects occur after daily *treatment* with 0 5 g of dihydrostreptomycin for 90 days In Cohen et al's (4) series of 149 patients treated with 1 g of dihydrostreptomycin daily for 120 days tinnitus or subclinical loss of hearing for high frequencies was observed in 25 % of the cases slight hearing impairment (5—20 decibels) in 12 % and moderate impairment (25—40 decibels) in 3 % An increase in the daily dose from 1 to 3 g raises the incidence of hearing disturbance from 16 % to 90 % according to the findings of Eckel and Altenburger (6)

The risk of ear damage from the use of streptomycin or dihydrostreptomycin can be reduced considerably if treatment is given intermittently, with 1 g 2 to 3 times a week (21)

Kanamycin mainly causes cochlear damage which may lead to rapid deterioration of the hearing Bunn et al (2) recommended that the total dose of kanamycin should not exceed 40 g in order to ensure that no side effects would arise Finegold et al (8) considered that a dosage of 15 mg/kg body weight per day has an adequate effect and ensures relative freedom from risks Impaired renal *function may lead to* increasing serum concentration of the drug and consequently also an increased risk of hearing disturbance (23) The daily dose should therefore be *modified* in accordance with the state of the renal function and a close watch kept on the serum concentration (7)

Neomycin, when *given parenterally, causes* damage to the cochlea and the kidneys

Greenwood (13) assembled from the literature a series of about 20 cases with grave *hearing loss following neomycin therapy* Parenteral administration of neomycin in desperate situations has become less common since kanamycin, which has practically identical antibacterial properties but is less toxic, became available

Viomycin may cause impairment of hearing and disturbance of equilibrium, and is also nephrotoxic (30 35) According to Werner et al (35) 2 g of viomycin daily considerably increases the risk of side effects Pitts et al (25) found that 2 g every third day for 4 months caused vertigo or tinnitus in 11 % of his cases and that in no case was there any objectively demonstrable ear damage Impairment *of the renal function occurred* in 16 % of the cases

Vancomycin which is usually given by in*travenous injection or drip* may give rise to hearing disturbances Dutton and Elmes (5) and Geraci et al (11) using a dosage of 1—2 g daily, noted rapid deterioration of hearing in patients with impaired renal function In the patients with hearing disturbance described by Geraci *et al* the serum concentrations of vancomycin had risen *to* 80—100 mcg/ml According to Geraci et al the toxic serum level of vancomycin *is* not known Most infections can be controlled with levels of 20—40 mcg ml Dutton and Elmes (5) treated an anuric patient with reduced doses of *vancomycin* The serum levels were kept below 20 mcg ml and severe hearing loss was avoided

The occurrence of ototoxic side effects has thus been placed in relation to the size of the daily dose the duration of treatment, and increasing blood levels of the antibiotic because of slowed elimination due to renal failure General principles for dosage with toxic antibiotics to patients with renal insufficiency have been outlined by Kunin and Finland (19) on the basis of studies of the halflife time of antibiotics in the blood in patients with normal renal function and with anuria A scheme for kanamycin dosage in patients with different degrees of renal failure has been tried out by Erlanson et al (7)

The present investigation is an analysis of a series of patients with ototoxic side effects following treatment with streptomycin dihydrostreptomycin and kanamycin It aims at throwing light on factors likely to have produced the lesions and on possible ways of preventing them

Material

The series consists of 37 patients 9 men and 28 women whose ages ranged from 22 to 79 years (average age 57 years) and who were examined at the Ear Nose and Throat Clinic at Lund between 1958 and 1960 Most of them had been sent in for examination because of subjective symptoms which had arisen either during or immediately after antibiotic therapy In a few cases the connection between the streptomycin or dihydrostreptomycin therapy and the ototoxic symptoms had not been discovered until after the patient had himself sought assistance for his discomfort or when the hearing and balance were being tested as a routine preliminary measure before starting kanamycin treatment In some cases receiving kanamycin therapy the damage had been detected at the regular check ups made during the treatment

The most important clinical data are shown in table II Chronic pyelonephritis and different types of respiratory tract infection predominated among the clinical diagnoses that had led to antibiotic therapy The renal function had been assessed in 26 of the 37 patients and was found to be impaired in 21 Patient 29 had been treated at different periods with dihydrostreptomycin and kanamycin and patient 31 with dihydrostreptomycin and kanamycin

Methods

The otoneurological examination included a hearing test with tone audiometry, and testing of the organ of equilibrium by means of Fitzgerald and Hallpike's (9) caloric test, with water at exactly 30° C and 44° C for 40 seconds and recording of the induced nystagmus by electronystagmography according to Henriksson's (17) method

The renal function was assessed on the basis of the 24-hour creatinine clearance or urea clearance In a few cases with acute renal failure the only information available was that concerning the N P N

Results

A Side effects of streptomycin

Ototoxic symptoms following streptomycin sulphate therapy occurred in 23 cases and following streptomycin pantothenate in 5 cases As these lesions were of the same type and arose under similar circumstances with respect to dosage duration of treatment and the like, they have been grouped together

The subjective symptoms in the form of dizziness had appeared one week at the latest after cessation of treatment Of 19 patients with observation times of from 6 months to 6 years 13 had

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Antibiotic	Impairment of Balance	Impairment of Hearing	Kidney function
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According to Aschan s (1) experience no side effects occur after daily treatment with 0 5 g of dihydrostreptomycin for 90 days In Cohen et al s (4) series of 149 patients treated with 1 g of dihydrostreptomycin daily for 120 days, tinnitus or subclinical loss of hearing for high frequencies was observed in 25 % of the cases, slight hearing impairment (5—20 decibels) in 12 % and moderate impairment (25—40 decibels) in 3 % An increase in the daily dose from 1 to 3 g raises the incidence of hearing disturbance from 16 % to 90 % according to the findings of Eckel and Altenburger (6)

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TABLE II Case summaries (kidney function 24 hour creatinine clearance (ml/min) in most cases In a few cases other measures are given)

Pat no	Age sex	Clinical diagnosis	Drug	Kidney function	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Ototoxicity Symptoms	Ototoxicity Lesions
1	42 ♀	Tuberculous arthritis	STM	?	1	20	15	Vertigo at end of course	Caloric reaction lost bilaterally
2	62 ♀	Aural chondritis	STM	?	1 5	25	13 5	Vertigo at end of course	Caloric reaction lost bilaterally
3	71 ♂	Pneumonia	STM	?	2	33	24	Vertigo at end of course	Caloric reaction lost bilaterally
4	48 ♂	Renal tuberculosis and meningitis	STM	?	2–1 (1 7)	27–14 (20)	71	Vertigo after 30 days (50 g)	Caloric reaction lost bilaterally
5	57 ♂	Ext otitis Erysipelas	STM	?	2	38	10	Atypical vertigo after course	Caloric reaction lost on right side
6	73 ♂	Maxill sinusitis	STM	?	2	30	14	Vertigo at end of course	Caloric reaction weak on right side
7	79 ♂	*Prophylactic treatm* after cancer surgery	STM	?	2	36	10	Vertigo at end of course	Caloric reaction lost bilaterally
8	53 ♀	Osteitis *after operation* for meningeoma	STM	?	2	32	22	Vertigo at end of course	Caloric reaction lost bilaterally
9	46 ♂	Osteitis *after operation* for meningeoma	STM	?	2	28	32	Vertigo at end of course	Caloric reaction lost bilaterally
10	63 ♂	Otitis ext chron otitis media	STM	?	2	27	10	Vertigo at end of course	Caloric reaction lost bilaterally
11	37 ♂	Pulm tuberculosis	DHSM	?	1	14	*36	Tinnitus impaired hearing 2 weeks after course	Moderate perception deafness bilaterally

12	53	Chron pyelonephritis	STM	2 1	5 9	1	18	16	Vertigo at end of course	Caloric reaction lost bilaterally
13	67	Paratyphoid fever acute renal failure	STM + DHSM	5 5	34 4	1+1	15+15	5+5	Vertigo at end of course	Caloric reaction lost bilaterally
14	58♀	Chron pyelonephritis acute renal failure	STM	5 4		0 5−0 25	11 5−5 5 (6)	5	Vertigo at end of course	Caloric reaction lost bilaterally
15	22♀	Chron pyelonephritis	STM	7 4		0 25	5	6 75	Dimmed vision	Caloric reaction lost bilaterally
16	48♀	Chron pyelonephritis	STM	10 1		2−1 (1 4)	40−20 (28)	7	Vertigo at end of course	Caloric reaction lost bilaterally
17	62♂	Pulm tuberculosis Chron nephritis	STM + DHSM	14 4		0 5+0 5	7 5+7 5	*14 5+14 5	Vertigo at end of course	None
18	75♀	Chronic bronchitis renal failure	STM	20 4		1 5	25	7 5	Vertigo at end of course	None
19	55♀	Chron pyelonephritis	STM	*14 *1 014		1	21	8	Vertigo at end of course	Caloric reaction lost bilaterally
20	35♀	Pneumonia chron nephritis	STM	*42 *1 017		0 25	3	6	Vertigo at end of course	Caloric reaction lost bilaterally
21	69♀	Chron pyelonephritis	STM	21 5		1−0 2 (0 3)	17−3 (6)	4	Vertigo during course	Caloric reaction lost on right side
22	71♀	Bronch asthma chron renal failure	STM	48 6		1	20	8	Vertigo at end of course	Caloric reaction lost on right side
23	55♂	Otitis media	STM	94 7		2	30	14 7	Vertigo at end of course	Caloric reaction weak on left side
24	76♀	Susp oesophageal perforation	STM	97		2	33	14	Vertigo at end of course	Caloric reaction lost on right side
25	76♀	Pulmonary abscess	STM	120		1	15	*35	Vertigo at end of course	Caloric reaction lost on right side

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13	67♀	Paratyphoid fever *acute renal failure*	STM + *DHSM*	5.5 3.4	1+1	15+15	5+5	Vertigo at end of course	Caloric reaction lost bilaterally
14	58♂	Chron. pyelonephritis acute renal failure	STM	5.4	0.5 0.25	11.5 5.5 (6)	5	Vertigo at end of course	Caloric reaction lost *bilaterally*
15	?2♀	Chron. pyelonephritis	STM	7.4	0.25	5	6.75	Dimmed vision	Caloric reaction lost bilaterally
16	48♀	*Chron. pyelonephritis*	STM	10.1	2–1 (1.4)	40–20 (28)	7	Vertigo at end of course	Caloric reaction lost *bilaterally*
17	*62♂*	Pulm. tuberculosis *Chron. nephritis*	STM + *DHSM*	*14.4*	0.5+0.5	*7.5+7.5*	*14.5+14.5	Vertigo at end of course	None
18	75♀	*Chronic bronchitis renal failure*	STM	20.4	1.5	25	7.5	Vertigo at end of course	None
19	55♀	Chron. pyelonephritis	STM	*14 *1.014	1	21	8	Vertigo at end of course	Caloric reaction lost bilaterally
20	35♀	Pneumonia chron. nephritis	STM	42 *1.017	0.25	3	6	Vertigo at end of course	Caloric reaction lost bilaterally
21	69♀	Chron. pyelonephritis	STM	21.5	1–0.2 (0.3)	17–3 (6)	4	Vertigo during course	Caloric reaction lost on right side
22	*71♀*	*Bronch. asthma* chron. renal *failure*	STM	48.6	1	20	8	Vertigo at end of course	*Caloric* reaction lost on right side
23	55♂	Otitis media	STM*	94.7	2	30	14.7	Vertigo at end of *course*	Caloric *reaction weak on left side*
24	70♀	*Susp. oesophageal* perforation	STM	97	2	33	14	Vertigo at end of course	Caloric reaction *on lost* on right side
25	*76♀*	Pulmonary abscess	STM	120	1	15	*35	Vertigo at end of course	Caloric reaction lost on right side

TABLE II (cont)

Pat no	Age Sex	Clinical diagnosis	Drug	Kidney function	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Ototoxicity Symptoms	Ototoxicity Lesions
26	59 ♀	Infected varicose ulcers	STM	122	1 5	13	8 5	Vertigo at end of course	Caloric reaction weak on left side
27	42 ♂	Otitis media	STM	159	1 2	16	8 4	Vertigo at end of course	Caloric reaction weak on right side
28	51 ♂	Pleurectomy bronchopneumonia acute renal failure	STM	*60–80	1	15	14	Vertigo at end of course	Caloric reaction lost on right side
29	60 ♂	Chron pyelonephritis	DHSM	24 3	1	16	23	Impaired hearing 2—3 months after course	Moderate perception deafness bilaterally
			KM		0 4	7	25	Vertigo during course	None
30	31 +	Cholecystitis chron pyelonephritis	DHSM	32	1 –0 5 (0 8)	20–10 (15)	6	Impaired hearing 2—3 months after course	Moderate perception deafness bilaterally
31	46 ,	Chron pyelonephritis	DHSM		1	20	8 5	Impaired hearing after course	Moderate perception deafness bilaterally
			STM		1 5	30	10 5	Vertigo at end of course	Caloric reaction lost bilaterally
			KM	12–15	0 3–0 2 (0 25)	6–4 (5)	9 4	Rapid hearing loss at end of course	Deaf right side severe perception deafness on left side

32	38	Chron pyelonephritis	KM	21 27	0 5–0 1 (0 25)	8–1 8 (4)	21	Tinnitus *after 7 days disappeared* after reduction of *dose*	Perception deafness above 3 000 cps bilaterally
33	44	Chron pyelonephritis	KM	170–70	0 35	5 6	6 9	*None*	Perception deafness above 3 000 cps bilaterally
34	33 ♀	Septic abortion septicemia acute renal failure	KM	Anuria	0 5–0 2 (0 3)	10–4 (6)	8 1	Tinnitus impaired hearing vertigo	Perception deafness above 1 000 cps bilaterally Caloric reaction weak bilaterally
35	42 ♀	Chron *pyelonephritis*	KM	9	0 25–0 15 (0 2) 0 15	4–2 (3 6) 2 4	5 75 2	Tinnitus after first *course*	Perception deafness above 3 000 cps bilaterally
36	42 ♀	Chron pyelonephritis	KM	16	0 5	9 4	16	None	Perception deafness above 3 000 cps bilaterally
37	25 ♂	Cong heart disease acute renal failure *septicemia*	KM	Anuria	0 5	9	0 5	First 5 g in 10 days After 7 days *further* 0 5 g Immediate rapid hearing loss	Deaf right side severe perception deafness on left side Caloric reaction lost bilaterally

STM = streptomycin sulphate
DHSM = dihydrostreptomycin sulphate
STM — *streptomycin pantothenate* (Streptothenat©)
KM = *kanamycin*

[1] Urea clearance %
[2] Spec gravity
[3] NPN mg%
[4] *5 days daily and 120 days intermittent treatment*
[5] Intermittent treatment
( ) Mean dose

TABLE III Dosage and duration of treatment in 10 patients with vestibular damage due to streptomycin Kidney function not studied

Pat no	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Duration of treatment (days)
1	1	20	15	15
2[1]	1 5	25	13 5	9
3[1]	2	33	24	12
4	1 7	24	50	30
5[2]	2	38	10	5
6[2]	2	30	14	7
7	2	36	10	5
8	2	32	22	11
9	2	28	32	16
10	2	27	10	5
Mean (Range)	1 8 (1–2)	29 (20–38)	20 (10–50)	11 5 (5–30)

[1] Treated with streptomycin pantothenate
[2] Unilateral vestibular damage

TABLE IV Dosage and duration of treatment in 5 patients with unilateral vestibular damage due to streptomycin Normal kidney function

Pat no	Creatinine clearance (ml/min)	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Duration of treatment (days)
23[1]	94 7	2	30	14 7	7
24	97	2	33	14	7
25[2]	120	1	16	35	5 (+120 intermittent)
26[3]	122	1 4	13	8 5	6
27[1]	159	1 2	16	8 4	7
Mean (Range)	—	1 7 (1–2)	23 (13–33)	11 4 (8 4–14 7)	6 8 (6–7)

[1] Treated with streptomycin pantothenate
[2] Treated mainly intermittently Not included in calculation of mean values
[3] Marked obesity body weight 110 kg

transient dizziness lasting from one week to 4 months (on an average, 2 months) The other 6 patients still had symptoms of dizziness at the last examination carried out 1 5—6 years after their first appearance In 16 of the 28 patients the

TABLE V Kidney function dosage and duration of treatment in 11 patients with damage due to streptomycin and reduced kidney function

Pat no	Creatinine clearance (ml/min)	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Duration of treatment (days)
A Ordinary dose					
12[a]	2–6	1	18	16	16
13	6–34	1	15	5	5
16	10	1 4 (2–1)	28 (40–20)	7	5
19	(urea clearance 14%)	1	21	8	8
31	12–15[b]	1 5	30	10 5	7
22[1]	49	1	20	8	8
28[1]	Uraemia	1	15	14	14
Mean (Range)		1 1 (1–2)	21 (15–40)	10 (5–16)	9 (5–16)
B Reduced dose					
14	5	0 4 (0 5 0 25)	6 (12–5)	5	13
15	7	0 25	5	6 75	27
20	(urea clearance 42%)	0 3 (0 5 0 25)	3 (6–3)	6	25
21[1]	22	0 3 (1–0 2)	6 (17–3)	4	12
Mean (Range)		0 3 (0 2–1)	5 (3–17)	5 4 (4–6 75)	19 (19–27)

Unilateral vestibular damage
[1] Treated with streptomycin pantothenate
[b] Kidney function tested one year after treatment

caloric reaction was absent or impaired bilaterally and in 10 it could be recorded on one side only Two patients (nos 17 and 18) had subjective symptoms which passed off rapidly without objective signs of vestibular damage Table III gives the data concerning 10 patients with streptomycin lesions for whom the state of the renal function was not known There was nothing in the history of their illness however to suggest the presence of renal disease The renal function could be assessed in 18 patients with streptomycin lesions, 5 had normal clearance values (table IV) and 13 had definite functional impairment (table V)

The daily doses of streptomycin were exceptionally high — usually 1 5–2 0 g or calculated per kg body weight 29 and 23 mg respectively, on an average — in the two groups with proved normal and probably normal renal function Two of these patients (nos 1 and 25) hade received 1 g per day In case 1 however, the daily dose was 20 mg when calculated per kg body weight, a figure which is higher than the 15 mg/kg estimated for a daily dose of 1 g and a

TABLE II (cont.)

Pat no	Age Sex	Clinical diagnosis	Drug	Kidney function	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Ototoxicity Symptoms	Ototoxicity Lesions
26	59 ♀	Infected varicose ulcers	STM	122	1.5	13	8.5	Vertigo at end of course	Caloric reaction weak on left side
27	42 ♂	Otitis media	STM	159	1.2	16	8.4	Vertigo at end of course	Caloric reaction weak on right side
28	51 ♂	Pleurectomy bronchopneumonia, acute renal failure	STM	*60–80	1	15	14	Vertigo at end of course	Caloric reaction lost on right side
29	60 ♂	Chron. pyelonephritis	DHSM	24.3	1	16	23	Impaired hearing 2—3 months after course	Moderate perception deafness bilaterally
			KM		0.4	7	25	Vertigo during course	None
30	31 ♀	Cholecystitis chron. pyelonephritis	DHSM	32	1–0.5 (0.8)	20–10 (15)	6	Impaired hearing 2—3 months after course	Moderate perception deafness bilaterally
31	46 ♀	Chron. pyelonephritis	DHSM		1	20	8.5	Impaired hearing after course	Moderate perception deafness bilaterally
			STM		1.5	30	10.5	Vertigo at end of course	Caloric reaction lost bilaterally
			KM	12–15	0.3–0.2 (0.25)	6–4 (5)	9.4	Rapid hearing loss at end of course	Deaf right side, severe perception deafness on left side

[illegible]	39	Chron pyelonephritis	KM	21 27	0 5 0 1 (0 25)	8 1 8 (4)	21	Tinnitus after 7 days disappeared after reduction of dose	Perception deafness above 3 000 cps bilaterally
33	44	Chron pyelonephritis	KM	170 – 70	0 35	5 6	6 9	None	Perception deafness above 3 000 cps bilaterally
34	33 [illegible]	Septic abortion septicemia acute renal failure	KM	Anuria	0 5 – 0 2 (0 3)	10 – 4 (6)	8 1	Tinnitus impaired hearing vertigo	Perception deafness above 1 000 cps bilaterally Caloric reaction weak bilaterally
35	42 [illegible]	Chron pyelonephritis	KM	9	0 25 – 0 15 (0 2) 0 15	4 – 2 (3 6) 2 4	5 75 2	Tinnitus after first course	Perception deafness above 3 000 cps bilaterally
36	42 [illegible]	Chron pyelonephritis	KM	16	0 5	9 4	16	None	Perception deafness above 3 000 cps bilaterally
37	25 [illegible]	Cong heart disease acute renal failure septicemia	KM	Anuria	0 5	9	5 5	First 5 g in 10 days After 7 days further 0 5 g Immediate rapid hearing loss	Deaf right side severe perception deafness on left side Caloric reaction lost bilaterally

STM = streptomycin sulphate
DHSM = dihydrostreptomycin sulphate
STM = streptomycin pantothenate (Streptothenat®)
KM = kanamycin

[1] Urea clearance %
[2] Spec gravity
[3] NPN mg%
[4] 5 days daily and 120 days intermittent treatment.
[5] Intermittent treatment
() Mean dose

TABLE III Dosage and duration of treatment in 10 patients with vestibular damage due to streptomycin Kidney function not studied

Pat. no	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Duration of treatment (days)
1	1	20	15	15
2[1]	1 5	25	13 5	9
3[1]	2	33	24	12
4	1 7	24	50	30
5[2]	2	38	10	5
6[2]	2	30	14	7
7	2	36	10	5
8	2	32	22	11
9	2	28	32	16
10	2	27	10	5
Mean (Range)	1 8 (1–2)	29 (20–38)	20 (10–50)	11 5 (5–30)

[1] Treated with streptomycin pantothenate.
[2] Unilateral vestibular damage

TABLE IV Dosage and duration of treatment in 5 patients with unilateral vestibular damage due to streptomycin Normal kidney function

Pat no	Creatinine clearance (ml/min)	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Duration of treatment (days)
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24	97	2	33	14	7
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26[3]	122	1 4	13	8 5	6
27[1]	159	1 2	16	8 4	7
Mean (Range)	–	1 7 (1–2)	23 (13–33)	11 4 (8.4–14 7)	6 8 (6–7)

[1] Treated with streptomycin pantothenate
[2] Treated mainly intermittently Not included in calculation of mean values
[3] Marked obesity body weight 110 kg

transient dizziness lasting from one week to 4 months (on an average, 2 months) The other 6 patients still had symptoms of dizziness at the last examination carried out 1 5—6 years after their first appearance In 16 of the 28 patients the

TABLE V Kidney function dosage and duration of treatment in 11 patients with damage due to streptomycin and reduced kidney function

Pat no	Creatinine clearance (ml/min)	Daily dose g	Daily dose mg/kg wt	Total dose (g)	Duration of treatment (days)
A Ordinary dose					
12[1]	2–6	1	18	16	16
13	6–34	1	1.	5	5
16	10	1 4 (2–1)	28 (40–20)	7	5
19	(urea clearance 14 %)	1	21	8	8
31	12–15[2]	1 5	30	10 5	7
22[1]	49	1	20	8	8
28[1]	Uraemia	1	15	14	14
Mean (Range)		1 1 (1–2)	21 (15–40)	10 (5–16)	9 (5–16)
B Reduced dose					
14	5	0 4(0 5–0 25)	6 (12–5)	5	13
15	7	0 25	5	6 75	27
20	(urea clearance 42%)	0 3(0 5–0 25)	3 (6–3)	6	23
21[1]	22	0 3 (1–0 2)	6 (17–3)	4	12
Mean (Range)		0 3 (0 2–1)	5 (3–17)	5 4 (4–6 75)	19 (19–27)

[1] Unilateral vestibular damage
[2] Treated with streptomycin pantothenate
Kidney function tested one year after treatment

caloric reaction was absent or impaired bilaterally and in 10 it could be recorded on one side only Two patients (nos 17 and 18) had subjective symptoms which passed off rapidly without objective signs of vestibular damage Table III gives the data concerning 10 patients with streptomycin lesions for whom the state of the renal function was not known There was nothing in the history of their illness however to suggest the presence of renal disease The renal function could be assessed in 18 patients with streptomycin lesions 5 had normal clearance values (table IV) and 13 had definite functional impairment (table V)

The daily doses of streptomycin were *exceptionally high* — usually 1 5—2 0 g *or calculated per kg body weight*, 29 and 23 mg respectively, on an average — *in the two groups with proved normal and probably normal renal function* Two of these patients (nos 1 and 25) hade *received 1* g per day In case 1, however, *the daily* dose was 20 mg when calculated *per kg* body weight a figure which is higher than the 15 mg/kg estimated for a daily dose of 1 g and a

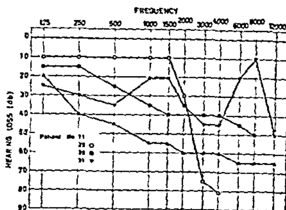


Fig 1 Audiograms of the best ear in four patients with impaired hearing after treatment with *dihydrostreptomycin*

body weight of 70 kg Patient 25 differed from the others in that she was treated daily for 5 days and then intermittently (2 to 3 times a week) for 4 months In patient 26, side effects developed despite normally functioning kidneys and a low daily dose — 14 mg — calculated per kg body weight, this patient, a woman with severe obesity, weighed 110 kg and her daily dose was 1 5 g

To avoid a possible cumulative effect, 4 patients (nos 14, 15, 20 and 21) in the group with renal insufficiency (table V) had been given reduced daily doses, on an average 0 3 g corresponding to 5 mg/kg body weight The other 9 patients with renal insufficiency had received 1—2 g per day, on an average 21 mg/kg

The average total dose was low — 20 g and 11 4 g, respectively in the two groups with proved or probably normal kidneys, and 10 g and 5 4 g respectively in the two groups with impaired renal function The treatment time was relatively short — on an average 11 5 days and 6 8 days, respectively, in the group with proved or probably normal renal function, and 9 days and 19 days, respectively, in the groups with kidney damage (cf tables III, IV and V)

B Side effects of dihydrostreptomycin

Ototoxic symptoms were noted in 4 cases Their audiograms are shown in fig 1 It is true that the group is small, but it is illustrative Patient 11 was treated for pulmonary tuberculosis, at first with daily doses, and then intermittently Within a few days of the termination of treatment an incapacitating hearing loss began The state of the renal function was not known in this case The other 3 patients had renal insufficiency Despite the presence of severe renal failures patient 29 was given 1 g daily for 23 days, 2 to 3 months after cessation of the drug a neurogenic hearing loss of moderate degree appeared Patient 30 was treated for cholecystitis, receiving 6 g in all over a period of 8 days She had had repeated attacks of cystitis, the urine was protein free and the N P N normal No further investigation of the renal function was carried out About 2 months after the treatment her hearing deteriorated and at that time the diagnosis of chronic pyelonephritis with impaired renal function (creatinine clearance 32 ml/min) was also established Patient 31 was treated for chronic pyelonephritis The creatinine clearance was c 15 ml/min and the body weight 50 kg A total dose of 8 5 g of dihydrostreptomycin was given over 9 days and this resulted in a gradual loss of hearing The last named two patients were treated with a combined preparation containing dihydrostreptomycin and penicillin

C Side effects of kanamycin

Ototoxic lesions were observed in 7 patients who were treated at the Medical Clinic (Renal Clinic) at Lund for chronic pyelonephritis or septicaemia with a bacterial flora resistant to other drugs (7) Another patient (no 29) had dizziness but no objectively demonstrable lesions As the possibility of ototoxic side effects was kept in mind from the beginning, the hearing was investigated regularly and the daily dose was adjusted to fit in with the renal function while at the same time assays of kanamycin blood levels were carried out The first patients treated (no 32, 33, 35 and 36) developed a mild hearing loss with reduced ability to distinguish high frequencies (fig 2) Some of the patients had tinnitus or a sensation of pressure or fullness in the ears, these symptoms disappeared when the dose of kanamycin was reduced or the drug was withdrawn altogether They did not complain of impaired hearing Patients treated at a later date were given doses that had been further reduced and side effects for the most part could then be avoided

Severe damage to the hearing arose in patient no 31 who had *pyelonephritis* and grave renal insufficiency She already had moderately impaired hearing caused by previous treatment with dihydrostreptomycin as well as total loss of the vestibular function caused by streptomycin Despite reduction of the daily dose an incapacitating hearing loss arose (fig 3) The serum concentrations of kanamycin were assayed regularly and did not rise above 38 mcg/ml Two oliguric anuric patients (nos 34 and 37 see fig 3) developed a severe loss of

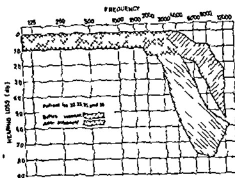


Fig 2 Audiograms before and after kanamycin treatment in four patients Hearing slightly impaired

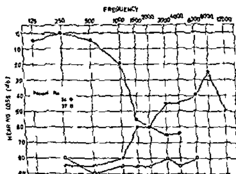


Fig 3 Audiograms of the best ear in three patients with severe loss of hearing after kanamycin therapy

hearing after treatment on vital indications for septicaemia, in connection with acute renal failure The daily doses were high in relation to the renal function and the kanamycin concentration in serum was not followed Dizziness as well as a greatly reduced or extinguished caloric reaction were observed in addition to serious damage to the hearing

Comments

The series presented here mainly consists of patients treated with daily doses of ototoxic antibiotics — streptomycin

dihydrostreptomycin, and kanamycin — for non-tuberculous infections for a relatively short period, in two thirds of the cases for only 5—14 days The *total dose* of the antibiotic is thus low, being less than 20 g in most of the cases, and 10 g or less in 22 cases Our findings do not lend support to Vogelsanger's (34) opinion that a total dose of 10 g in daily doses of one gram, is without danger The widely held view that total doses of streptomycin or dihydrostreptomycin not exceeding 40 g do not in general have toxic effects might possibly be justified in the case of intermittent dosage with 2—3 doses a week This scheme of dosage, which has been commonly accepted for the treatment of tuberculosis, appears to involve little risk of ototoxic side effects, although such lesions do sometimes occur (patients 17 and 25)

Impaired renal function was present in two-thirds of the patients — in 13 out of 28 with streptomycin lesions, in 3 out of 4 with dihydrostreptomycin lesions, and in all of those who had disorders caused by kanamycin Our experience emphasizes the important part played by renal insufficiency in the development of ototoxic lesions, a factor often mentioned in the literature but not always taken into full consideration in practice The importance of reducing the daily dose given to patients with renal insufficiency is also evidenced by the fact that streptomycin lesions appeared sooner with an ordinary dose than with a reduced dose (according to table V, after respectively 9 and 19 days, on an average) Our findings in connection with kanamycin therapy in chronic pyelonephritis show that with a reduced though still therapeutic dose, treatment can be continued over a relatively long period without causing any particularly severe hearing disturbance

In 13 patients with streptomycin lesions and probably normal renal function who had received short term therapy, the *daily dose* was on an average 1 8 g, corresponding to 28 mg/kg body weight All except one patient had received more than 1 g per day Our findings provided evidence in support of Vogelsanger's view that when streptomycin is given daily the daily dose should not exceed 1 g/70 kg or 15 mg/kg Since we have been using this dosage at the Ear, Nose and Throat Clinic at Lund, and have treated over 1,000 cases with acute infections for about 7 days, vestibular damage has been noted in only one case (no 27)

The occurrence of streptomycin lesions in patient 26 despite the fact that the daily dose was only 13 mg/kg body weight may possibly have had some connection with her obesity (weight 110 kg) Fat contains much smaller amounts of extracellular fluid than muscles and glands The extracellular fluid space over which streptomycin and similar antibiotics become distributed is consequently less in an obese person than in a person of ordinary build with the same body weight Hence a dosage scheme per kg of body weight presumably gives higher concentrations of streptomycin in the extracellular fluid in an obese person than in a thin muscular patient High body weight due to obesity should therefore be a reason for reducing the daily dose, calculated per kg of body weight

Streptomycin lesions are reported almost without exception as occurring bilaterally, but they may also occur unilaterally or show a high degree of asymmetry, as Cawthorne and Ranger (3), Stahle (32), and other investigators have pointed out In the present series, unilateral side effects were noted in 10 patients who had normal or only slightly impaired renal function and who had received relatively small doses of streptomycin

In Cawthorne and Ranger s (3) cases, as well as in ours, the treatment time was short, which presumably leads to a relatively large number of cases with mild toxic lesions and hence a greater likelihood that the vestibular damage will only be unilateral, or markedly asymmetrical

Our findings provided confirmation that *dihydrostreptomycin* therapy may cause incapacitating loss of hearing which may manifest itself several months after cessation of the drug The view that dihydrostreptomycin is less toxic than streptomycin receives support in the present series from the fact that a combined preparation with equal amounts of streptomycin and dihydrostreptomycin only caused vestibular damage (patients 13 and 17) Such a preparation has been said to be less toxic than one or the other of these drugs (16 26) it has however been found that it can cause not only vestibular damage as in our cases but also the late hearing dysfunction that follows dihydrostreptomycin (31)

According to the recommendations of the Food and Drug Administration in the U S A (10) dihydrostreptomycin should only be given when streptomycin is not tolerated A combination of dihydrostreptomycin and streptomycin should be reserved for tuberculous patients who do not tolerate full doses of streptomycin Dihydrostreptomycin in fixed combination with a non ototoxic agent such as penicillin, which was given to 2 patients in our series, has caused many hearing disturbances (31) and should be reserved for veterinary medicine (27)

The observation made by some investigators, suggesting that *streptomycin pantothenate* and *dihydrostreptomycin pantothenate* are less toxic than the corresponding sulphates (18) was not confirmed by the present series Our experiences in this respect were similar to those reported by others (cf 20 28)

The ototoxicity of *kanamycin* was reflected in a characteristic loss of hearing, which first applied to frequencies higher than 3 000 c p s and in some cases rapidly led to incapacitating deafness In only about half of the cases was the disturbance preceded by tinnitus or a sensation of pressure and fullness in the ears In some patients the hearing impairment remained unchanged despite the fact that the treatment was continued for 2 to 3 days after the drug had been withdrawn probably due partly to slow elimination of the drug In none of our patients with kanamycin lesions did the hearing disorder progress for any length of time after termination of treatment nor appear for the first time long after cessation of the drug as was the case with dihydrostreptomycin

Side effects appeared even after total doses of 5—6 g of kanamycin Five of

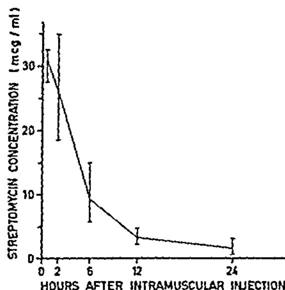


Fig 4 Streptomycin concentration in plasma after intramuscular injection of 1 g streptomycin sulphate Mean values of determinations in 9 adult males (Erlanson Own observations)

the 7 patients had received less than 10 g Like Finegold et al (8), we found that a maximum for the total dose, either of 40 g (2) or smaller quantities, is of no practical value in preventing lesions

The ototoxic symptoms in our patients usually arose after a short period of treatment with relatively high daily doses In most of the cases the renal function was impaired Thus high concentrations of the antibiotic in the extracellular fluid due to large doses and/or delayed elimination of the antibiotic was presumably the main factor underlying the changes Our material gave no information concerning the part played by other factors such as large total doses, advanced age ototoxic lesions from earlier treatments, poor general health, and the like

Accordingly, an important measure for preventing ototoxic side effects in connection with a daily dosage scheme is to adjust the doses so that the serum concentrations of the drug do not rise to too high levels An amount of 1 0 g streptomycin or kanamycin administered intramuscularly to a normal person weighing 70 kg gives a maximum serum concentration of 25—35 mcg/ml 1 to 2 hours after injection, after 12 hours the concentration drops to 2—5 mcg/ml (cf fig 4) 0 5 g intramuscularly gives a maximum serum concentration of 15—25 mcg ml after 2 hours

As the daily dose, according to clinical experience, should not exceed 1 g in a person weighing 70 kg, it may be assumed that the maximum concentration in the serum should not be higher than about 25 mcg/ml When the renal function is impaired the daily dose of the drug must be reduced, to prevent the maximum concentration from rising above 25 mcg/ml because of delayed elimination The level should also fall below 5—10 mcg/ml before the next injection is given A suitable dosage scheme for patients with impaired renal function

TABLE VI Dosage scheme for treatment with daily doses of kanamycin or streptomycin If creatinine clearance is about 20 ml/min or lower, larger doses, 0 4—0 3 g, given every second day are often preferable

Kidney function (24 hour creatinine clearance ml/min)	Daily dose	
	g/70 kg wt	mg/kg wt
1 Normal	0 5×2	15
2 80—51	0 5×1	7 5
3 50—25	0 25—0 3×1	3—4
4 24—15	0 15—0 2×1	2—2 5

has been tried out for kanamycin (7) (Cf table VI) In view of the pharmacological similarities between kanamycin and streptomycin the same dosage scheme was tried at the Medical Clinic B (Renal Clinic) for streptomycin therapy and proved to give approximately the same blood levels

Normal N P N values in the blood do not exclude the possibility of impaired renal function Hence, before streptomycin or kanamycin are given the renal function should be assessed by a suitable test e g the 24 hour creatinine clearance The suitability of the dosage decided upon on the basis of these findings should be checked by assay of the serum concentration of the drug

If symptoms of dizziness arise during streptomycin therapy the treatment should be broken off immediately and an otoneurological check up undertaken In urgent cases the treatment could be continued with a reduced dose

Kanamycin therapy should be preceded by an otoneurological examination especially when renal function is impaired The hearing should then be tested once a week by audiometry This allows any damage to the hearing to be detected before subjective symptoms arise If the audiogram shows any signs of hearing loss or if ototoxic symptoms arise tinnitus a sensation of pressure or fullness hearing impairment) the drug should be withdrawn or if urgent indications for its use are at hand given in a reduced dose The principles outlined here for dosage and regular check ups during treatment may probably be applied also to other antibiotics causing hearing dysfunction

Summary

Thirty seven patients with ototoxic side effects following treatment with streptomycin (28 cases), dihydrostreptomycin (4 cases), and kanamycin (7 cases) were examined at the Ear Clinic at Lund between 1958 and 1960 Two patients had been treated with both streptomycin and dehydrostreptomycin The lesions arose after treatment with daily doses in the majority of the cases to relieve non tuberculous infections The duration of treatment was remarkably short being 5—14 days in two-thirds of the cases, and the total dose was low, 4—10 g in two-thirds of the cases The daily dose was in most cases relatively large, 1 5—2 g corresponding to 20—28 mg per kg of body weight Two thirds of the patients had impaired renal function Reduction of the daily dose, which was applied in approximately half of these cases made it possible to carry out treatment for a longer period than was possible with an ordinary dose

Ten of the 26 patients treated with streptomycin only had unilateral or markedly asymmetrical vestibular damage, an effect that has previously only been observed in a few cases The patients with dihydrostreptomycin lesions developed hearing loss several months after treatment had been concluded The side effects of kanamycin first appeared in the form of a lowered threshold for high frequencies without subjective loss of hearing in half the cases the dysfunction was preceded by tinnitus or a sensation of pressure or fullness Serious effects were noted in three patients two of whom had acute and the third severe chronic renal insufficiency

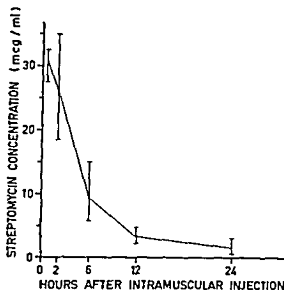


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As the daily dose, according to clinical experience, should not exceed 1 g in a person weighing 70 kg, it may be assumed that the maximum concentration in the serum should not be higher than about 25 mcg/ml When the renal function is impaired the daily dose of the drug must be reduced, to prevent the maximum concentration from rising above 25 mcg/ml because of delayed elimination The level should also fall below 5—10 mcg/ml before the next injection is given A suitable dosage scheme for patients with impaired renal function

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Kanamycin therapy should be preceded by an otoneurological examination especially when renal function is impaired The hearing should then be tested once a week by audiometry This allows any damage to the hearing to be detected before subjective symptoms arise If the audiogram shows any signs of hearing loss or if ototoxic symptoms arise (tinnitus a sensation of pressure or fullness hearing impairment) the drug should be withdrawn or if urgent indications for its use are at hand given in a reduced dose The principles outlined here for dosage and regular check ups during treatment may probably be applied also to other antibiotics causing hearing dysfunction

Summary

Thirty seven patients with ototoxic side effects following treatment with streptomycin (28 cases), dihydrostreptomycin (4 cases), and kanamycin (7 cases) were examined at the Ear Clinic at Lund between 1958 and 1960 Two patients had been treated with both streptomycin and dehydrostreptomycin The lesions arose after treatment with daily doses, in the majority of the cases to relieve non tuberculous infections The duration of treatment was remarkably short being 5—14 days in two-thirds of the cases, and the total dose was low 4—10 g in two-thirds of the cases The daily dose was in most cases relatively large, 1 5—2 g corresponding to 20—28 mg per kg of body weight Two-thirds of the patients had impaired renal function Reduction of the daily dose, which was applied in approximately half of these cases, made it possible to carry out treatment for a longer period than was possible with an ordinary dose

Ten of the 26 patients treated with streptomycin only had unilateral or markedly asymmetrical vestibular damage, an effect that has previously only been observed in a few cases The patients with dihydrostreptomycin lesions developed hearing loss several months after treatment had been concluded The side effects of kanamycin first appeared in the form of a lowered threshold for high frequencies without subjective loss of hearing in half the cases the dysfunction was preceded by tinnitus or a sensation of pressure or fullness Serious effects were noted in three patients two of whom had acute, and the third severe chronic renal insufficiency

Our findings emphasize the importance of individual adjustment of the daily dose to avoid too high serum and tissue concentrations of the antibiotic When the renal function is normal the daily dose should not exceed 1 g/70 kg or 15 mg/kg body weight Where renal function is impaired the daily dose should be reduced and the aural function and serum concentration of the antibiotic assessed A dosage scheme for patients with impaired renal function is suggested

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Megaloblastic Anaemia and Myxoedema in a Patient Suffering from Myeloma, Observed for a Period of 16 Years

By

J Bichel

It is well known that myelomatosis is a universally fatal disease with a very poor prognosis as to the survival time after the onset of symptoms On the basis of cases reviewed in the literature Snapper finds that the average duration of life between the initial symptoms and death is from 18 months to two years In his own large material Snapper found an average survival time of 20 months However the majority of his patients lived less than 18 months One single patient survived for eight years A period of this length is however an exception The longest survival time recorded in literature is reported by Coley (1) who found a single patient with a survival time of 15 years among 200 patients from Memorial Center There was no mention made of the case history

At the Radium Centre for Jutland we have had the opportunity of observing a patient with myelomatosis for 16 years

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As the survival time of this patient was exceptionally long and as her disease presented some peculiarities uncommon in myelomatosis, a short case report may be justifiable

It must be noted preliminarily, that besides her protracted myelomatosis the patient had a classic pernicious anaemia which was diagnosed shortly after she was referred to the clinic for the first time A few years later the patient developed typical myxoedema which responded adequately to thyroidine

Case report

On her first admission to the Radium Centre for Jutland in July 1947 the patient a married woman of 68 had been transferred from another hospital (Marselisborg Hospital) where she had been treated for an enteritis of brief duration During this admission achylia was diagnosed by several test meals (Ewald) Because of a persistent very high sedimentation rate (about 100 mm/hour) sternal puncture was done and

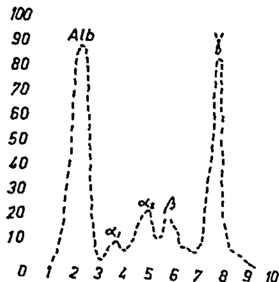


Fig 1 Electrophoretic pattern of the proteins in the serum Total protein 7 55

it was examined at the Radium Centre (by the author) At this first examination of the marrow about 14 5 % plasma cells were found in the smears, and several atypical plasma cells, which were rather large cells with a comparatively large, slightly ec centric nuclei *A few binuclear plasma cells* were also found The patient, therefore, was transferred to the Radium Centre to be treated for myeloma

On admission, her appearance was found to correspond with her age Her nutritional state was normal There seemed to be no *anamnestic information of any interest* apart from the fact that her hair had turned white very early in life

The plasmocytosis of the marrow with atypical plasma cells remained almost unchanged throughout the whole period of observation (1947—1963)

In June, *1950 about three years after the* myelomatosis had been diagnosed it was noticed that the patient had started gaining weight rapidly At the same time she had the appearance of a patient with myxoedema Her skin became dry, myxoedematous , her features somewhat coarser and her voice very rough *almost like a man s voice* She also began to complain of feeling constantly cold The basal metabolic rate was then about 80 % Thyroidine was then given together with anti pernicious therapy The former had a good effect on most of the symptoms which might be supposed to arise from the myxoedema It was also tried to discontinue the thyroidine periodically In *each case this resulted in a recurrence of the* myxoedematous symptoms

Numerous electrophoretic examinations of the patient s serum constantly revealed a very high, pointed gamma component (fig 1) The total protein in serum was as a rule between 7 and 8 g% The urine was ex amined at intervals for Bence Jones protein with negative results On investigation of *the serum in the analytic ultra centrifuge* no trace was found of macroglobulins. However, we had not the opportunity of making all the investigations we should have liked, as she died — shortly before we had intended to publish her case — in another hospital in May, 1963, 16 years after the disease had been diagnosed

The diagnosis of myeloma was verified by *the findings of atypical plasma cells* in the marrow in connexion with the persistent typical electrophoretic pattern

The patient's pernicious anaemia

As mentioned above the patient was transfer red to the Radium Centre for Jutland in July 1947 Already shortly after admission a marked megaloblastic erythro- and gra *nulopoiesis could be demonstrated in smears* of the bone marrow On review of previous smears taken a few months before it ap peared that a partial, but not distinct megaloblastic dysplasia was already percep tible On admission she had a hyperchromic anaemia and slight granulocytopenia Her tongue was red *but perhaps less smooth than* often seen in pernicious anaemia Since then (i e since 1947) she was treated with anti pernicious therapy mostly purified liver extract (hepsol fortior) but for a short time, folic acid (tabl folicae) was given Her anae mia responded favourably to the treatment *giving a typical reticulocyte response* to both An attempt was made to discontinue the therapy at times but each time her

megaloblastic anaemia manifested itself again so that there can be no doubt that she suffered from an anaemia demanding anti pernicious treatment

Discussion

Reports of megaloblastic marrow in myelomatosis are very rare the anaemia is generally stated as normoblastic Wintrobe (12) mentions that one of his patients who suffered from myeloma had a hyperchromic anaemia which at first was thought to be megaloblastic However on closer examination, it was found to be macroblastic During anti pernicious treatment such cases may show some reticulocyte increase, but no change in the haemoglobin level

As mentioned, Wintrobe s case was not a case of megaloblastic, but rather of macrocytic anaemia Dvoràk (3), however mentions a patient, a woman with a goitre which proved to be a plasmocytoma The bone marrow was megaloblastic but there was no histamine refractory achylia Protto (9) mentions a man of 55 with myelomatosis and hypochromic anaemia which in the last stage became hyperchromic with megaloblasts seen in the marrow Heilmeyer (4) considered it nearly always possible to find a few megaloblasts in the bone marrow in myelomatosis In his opinion the conditions here will be similar to those in acute leukaemia (so-called Aufbrauchpernicios a) Tousek and Vortel 11) have also found megaloblastic anaemias in myelomas In the present case it is tempting to connect the megaloblastic anaemia with the myxoedema although the latter was only observed three years afterwards

In myxoedema a megaloblastic anaemia of the Addisonian type may occur This is widely believed to be due to the coincidental occurrence of pernicious anaemia and myxoedema in the same patient (2) It has been suggested, however, that the incidence of these two conditions occurring together is too high for it to be explained in this way (8), and that the anaemia may in some cases be caused by gastric dysfunction occurring as part of the general depression of tissue activity in the hypothyroid state However in Mean s (7) monograph of 1941 the author tates 'We cannot say that the association is more than accidental Indeed we are inclined to believe that it is not'

The present case has been recorded

1 Because a survival time of this length is quite exceptional for patients with myelomatosis The long survival of the patient cannot be due to any specific treatment of the myelomatosis, as, in fact this disease was not treated at all

2 Because of the combination of a megaloblastic anaemia with myelomatosis It is often stated that the anaemia in myelomatosi may be more or less macrocytic but not megaloblastic

3 Finally, this case is mentioned because beside myelomatosis and pernicious anaemia the patient also suffered from myxoedema

Summary

Report on a case of myeloma combined with megaloblastic anaemia and myxoedema observed for a period of 16 years

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A Mass Survey to Trace Previously Unknown Diabetes Mellitus

A Preliminary Report

By

Arne Munke

On the initiative of the late Dr B Schersten (19) a mass examination for diabetes took place in 1958—1961 in the county of Blekinge The survey was supervised by him and later by the author

The purpose of the survey

a To determine the incidence of diabetes in the county of Blekinge (one of the smallest counties in Sweden — population 145 000)

b To appraise the technique and methods used in mass surveys for the tracing of previously unknown diabetes

c To discover early cases of diabetes so that through early treatment the progression and complications of the disease may be avoided

Method

I Collecting of material

Several years X ray examinations were started to detect tuberculosis among the Swedish population Such examinations are planned and supervised by the Royal Medical Board The examination was carried out as follows — On cards sent out by the Medical Board the Registration Office of the County Administration first fill in data concerning the county population over the age of 10 Information about time and place for the examination is given on the cards Each person called to examination brought his card The mass X ray examination took place in schools assembly halls or other suitable places within the centres of the various districts where the X ray patrol had been directed The diabetes examination was linked to this organisation as a result of a recommendation to the county council made by the Swedish Diabetes Association In the first place the diabetes survey aimed at testing the urine for glucose after a meal rich in carbohydrates In order to get data amenable to statistical work from such a survey it had to be simple but well organized The county council first appointed a central committee with one executive member The latter then appointed local committees in the various towns and communities It was extremely important that the local committees contained persons who were interested in social work. The local committee divided up its district into smaller districts which were of various sizes according to the number of inhabitants and the leaders of the

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districts then appointed block leaders Each block leader had about 200 persons within his block He was to call on people at their homes and hand over various instructions and information Each person received a personal letter that he or she was expected to appear at a stipulated time for a joint X ray and diabetes examination The X ray cards from the Royal Medical Board — a double card comprising one examination card and one summons card — were provided, on the back of the summons card, with special questions concerning the diabetes survey

The questions were as follows

1 Have you got diabetes?

2 For how many years have you had the disease?

3 Do you know of any case of diabetes in your family? If so, in whom?

4 Who is treating you? Doctor Hospital

5 Have you been a patient in a hospital because of this illness? What hospital?

Every person was requested to fill in the above mentioned form before appearing at the combined X-ray and diabetes examination Furthermore, each person was instructed how to deal with the urine specimen The text of that instruction read as follows

1 Bring a urine specimen in a small thoroughly cleaned bottle when you attend the mass X-ray examination (Note! The bottle should not be cleaned with synthetic detergents such as Surf Radion, Lita, Sulfo and Tend) One tablespoonful of urine is sufficient Attach to the bottle the label with your name and address filled in, which you received together with the summons to attend the mass X ray survey This is imperative in order that no mistakes be made

2 The urine specimen should be passed 2—4 hours after an ordinary meal, consisting of e g bread, potatoes sugar, jam, porridge or flour dishes etc

3 Fill in the questionnaire about diabetes on the back of the summons card

4 If any one of your family, owing to illness, invalidity etc , cannot attend the X ray examination, bring a urine specimen from this family member too, so that he or she is in any case examined as to diabetes

5 At the place of the examination you will give the summons card and the urine specimen to the card distributor, who will see to the rest of the examination You will get the bottle back when you have been X rayed and you will then also be informed about the result of the sugar examination

This system proved to work well Only in few cases was the equipment brought by the patrol made use of for taking urine specimens However, it was necessary to have this equipment at hand, especially on those occasions when there appeared to have been deficient cleaning of the bottles and a new specimen had to be taken The equipment was also needed in factories and schools etc where bottles were not available As only one X ray patrol was available, the examination ranged over a period of 3 years, and therefore many cards would have become obsolete by the time of the examination The printing of the cards was accordingly done in 3 stages and during this time some of the cards were continually re printed The combined X ray and diabetes survey in the county of Blekinge started on March 31st 1958 in the parish of Jamjo, and was finished on November 25th 1960 For those who, for some reason or other, had not appeared at the first examination special summons forms, including questions concerning both the X ray and the sugar survey, had to be printed and distributed This examination continued till the 22nd of March 1961 As a rule examinations were held between 2 and 4 p m and between 5 and 8 p m On the average 201 persons a day were examined During the time of the final examinations, it was stated over the radio and TV and in the press that in the future mass X ray surveys would no longer be necessary This, of course made the result worse as fewer of those called in for the examination presented themselves

2 Laboratory technique

a Urine analysis

Those who attended the diabetes examination brought a urine specimen that had been

passed 2—4 hours after a meal rich in carbohydrates. The urine was examined for glucose with clinistix. This was carried out immediately after the delivery of the bottle containing the urine specimen so that the person examined could at once be informed about the result of the sugar analysis.

Clinistix is a specific qualitative test for glucose based on the fact that the enzyme glucose oxidase in the presence of atmospheric oxygen oxidizes glucose to gluconic acid and hydrogen peroxide. The enzyme peroxidase splits the latter into water and oxygen and the oxygen with orthotolidin present turns it blue. The required enzymes are present in dry form on especially prepared slips of filter paper and the test is carried out by dipping one of the slips into the urine. If the paper is coloured blue within one minute glucose is present. The sensitivity limit is between 0.01 and 0.1 %, which is sufficient for clinical use. Packer and Ackerman (16) have compared these enzyme tests with Benedict's qualitative solution and have found clinistix superior for detecting diabetes in mass surveys (3, 5, 20).

b. Blood analysis

All those persons whose urine specimen showed a positive clinistix reaction in this mass survey were registered at the Medical Department of the county hospital in Karlskrona. They were later asked to appear at the clinic for closer examination. If the suspicion of diabetes was strong in individual cases — the disease might e.g. exist in the family or in relatives — those cases were called in first. Those who were asked to attend the examination were told to come in the morning on an empty stomach and to bring a specimen of the morning urine. Fasting blood sugar was first determined and the urine specimen was examined with clinistix for its glucose content. If the result was positive, a quantitative analysis with Clinitest was made. Every specimen showing glycosuria was examined for ketone bodies with Acetest or Rothera's test.

If the fasting blood sugar was so high as to prove diabetes generally no glucose tolerance test was carried out. If the fasting blood sugar was normal or only slightly above normal a glucose tolerance test was made. The persons on whom glucose tolerance tests were made had been told to eat their usual food the days before the test and to attend fasting on the morning of the day of examination. The glucose tolerance tests were conducted as follows. Fasting blood sugar was taken and then glucose dissolved in 250—300 ml water, 1 g/kilo of weight, was given per os. Every fifteen minutes during the next 2—3 hours a blood specimen was taken for sugar determination. Urine specimens were collected before the test, after one hour and again after two hours. Capillary blood was used at this test. The blood sugar was determined by Crecelius Seifert's colorimetric method. This method measures besides glucose other reducing substances such as ergothionine and glutathione.

In spite of the fact that glucose tolerance tests have been made for very many years there is no agreement regarding their value, how they should be best carried out or on what criteria the diagnosis diabetes should be based. Many factors need attention when glucose tolerance tests are made. The diet before the glucose tolerance test is of great importance. Sweeney (22) has revealed that a strict diet free from starch and maintained for several days causes a decreased glucose tolerance. A diet containing 20 g carbohydrate has the same effect according to Conn (4). Himsworth (9) points out that a supplement of 125 g glucose a day is sufficient to make the glucose tolerance curve normal. It is very unlikely that a person on a normal diet consumes less than 125 g carbohydrate a day. Wilkerson et al. (24) are of the opinion that an adequately nourished person does not need

districts then appointed block-leaders Each block leader had about 200 persons within his block He was to call on people at their homes and hand over various instructions and information Each person received a personal letter that he or she was expected to appear at a stipulated time for a joint X-ray and diabetes examination The X-ray cards from the Royal Medical Board — a double card comprising one examination card and one summons card — were provided on the back of the summons card, with special questions concerning the diabetes survey

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The level of the blood sugar curve after 1 hour has previously been reckoned very important when judging whether diabetes is present or not The level of the blood sugar curve after 1 hour, however, so often deviates from normal that in itself it cannot be regarded as reliable in evaluating the glucose toler ance test Mosenthal and Barry (15) say Our experience in a follow up series failed to show diabetes in high curves without other abnormality ' The blood sugar level 2 hours after addition of glucose is considered by all to be of the greatest importance, but there is no agreement as to the normal upper limit The American Diabetes Association recommends in Diabetes Guidebook for the Physician of 1956 that the true blood sugar value must fall to 120 mg/100 ml after 2 hours to guarantee absence of diabetes If the two-hour blood sugar is above 140 mg/100 ml the diagnosis diabetes is made What is most characteristic of the glucose tolerance curve in the case of diabetes is the delayed return to normal values

The evaluation of the glucose toler ance tests in this big examination there fore involved certain difficulties After critical reading of the literature with due regard to the method employed the following criteria for making the diagnosis diabetes were laid down

Fasting blood sugar 120 mg/100 ml
1 hour value 210 mg/100 ml
2 hour value 130 mg/100 ml
3 hour value 120 mg/100 ml

If at least two of these values were too high the diagnosis diabetes was made As mentioned before regard was paid to the food eaten the days just before the glucose tolerance tests Furthermore tobacco-smoking was forbidden just before and during the glucose tolerance tests

Results

At the census of 1960, the county of Blekinge had a population of altogether 144 468 — 72,647 men and 71 821 women During the last few years the population has been particularly constant About 65,000 people live in towns and about 80 000 in rural districts 122,476 persons were called in for the combined X ray and sugar examination Children up to the age of 10 were not examined at the X ray survey and consequently not at the sugar examination either Diabetes mellitus is a rare disease in children of these ages and it is likely that few cases of the illness are latent because symptoms in childhood diabetes are so pronounced that the disease is easily recognized Among the children up to 10 years of age (21 000) the frequency of diabetes is about 0 8 per thousand in the county of Blekinge 101,375 persons attended the X ray survey which is 82 7 % of those called in 97 862 persons appeared for the diabetes examination, which means 80 % of those called In the group of persons examined for diabetes there were 846 previously known diabetics Some of these known diabetics did not deliver urine specimens for analysis of sugar but of the urine specimens delivered by 588 known diabetics, the clinistix test showed a positive reaction in 434, while 154 were clinistix negative The clinistix was negative in 26 % of the tested known diabetics In

TABLE I Criteria for glucose tolerance tests All values in mg/100 ml

	Conn & Fajans (4)	Criteria most used in U S A after Mosenthal (14)				O Hanssen, Scandinavian countries (7 a 20)
	Venous blood			Capillary blood	Lawrence (11 a)	
Time after glucose	True blood sugar method (100 g)	Method of Folin Wu (100 g)	True blood-sugar method (100 g)	Method not specified (100 g)	Method not specified (50 g)	Method of Hagedorn Jensen (1 g/kg body weight)
Fasting	100	120	100	120	120	110
1 hour	160	170	150	200	200	220
2 hours	110	120	100	120	120	—
3 hours	—	—	—	—	—	*110*

a particularly large supplement of carbohydrates before an oral glucose-tolerance test

Blotner (2) found a decreased glucose tolerance in patients who had been in bed for a long period In some who later resumed normal activity, glucose tolerance became normal again Investigations by many authors e g Spence (21), Hale-White and Payne (7), Porter and Langley (18), and Malmros (13) have shown that glucose tolerance decreases with increasing age Mosenthal (14) could not confirm decreased glucose tolerance in aged persons Jorde (10) showed that with advancing age there is a clear tendency towards reduced glucose tolerance both in normal-weight and in overweight persons Lundberg and Thyselius-Lundberg (12) have pointed out that immediately after a person has started to smoke the blood sugar rises quickly to 50 % above the initial value A peak is reached during the smoking, then the blood sugar decreases somewhat more slowly In the course of half an hour the blood sugar level has fallen to its normal value If diabetes exists the reaction is stronger

Many pathological conditions can influence the glucose tolerance, for example hypothalamus disorders, acromegaly, Cushing's syndrome, pheochromocytoma, thyrotoxicosis, infections and liver diseases

Table I gives a survey of various criteria employed in judging the glucose-tolerance curve Different authors generally agree as far as the fasting blood sugar value is concerned, it is usually reckoned *that this must not exceed* 120 mg/100 ml An increased fasting *blood sugar is a reliable indicator* for the diabetes diagnosis A normal fasting blood sugar however does not in any way *exclude* a diabetes diagnosis

TABLE III Summarized results of the blood sugar levels in 372 new diabetics at the time of the diagnosis

	257 cases diagnosed by glucose tolerance tests		115 cases diagnosed by the fasting blood sugar values	
	Blood sugar level (mg/100 ml)	No of cases	Blood sugar level (mg/100 ml)	No of cases
Fasting	<120	51	140–199	23
	120–149	78		
	>150	128	200–249	26
Peak	180–249	66		
	250–299	79	250–299	36
	>300	112		
2 hours	130–149	10	300–399	28
	150–199	46		
	>200	114	>400	2

In 87 cases the $1\frac{1}{2}$ or $1\frac{3}{4}$ hour values at the glucose tolerance test were so high that no 2 hour values were determined

and the urine sugar determinations 257 were diagnosed with the further help of glucose tolerance tests Table III gives a summary of the blood sugar levels in these two groups

Doubtful cases

There were 81 persons in whom the glucose tolerance test showed values which although not proving diabetes were suspect These persons are now subject to further observation but no cases of manifest diabetes have as yet occurred in this group The intention is to examine this group with further glucose tolerance tests later

Glycosuria

In the examined population glycosuria was detected in 1 593 out of the 97,604 persons who had been tested with clinistix 258 known diabetics were not tested with clinistix Of the known diabetics who had been tested with clinistix, i e 588 persons, 154 were clinistix negative, or 26 % of these diabetics The frequency of glycosuria in the tested population was 1 6 % If we exclude the known diabetics from the total number of clinistix positive cases there were 1,156 unexplained cases of glycosuria 854 of which were more closely analysed and 372 of which turned out to be due to previously undiagnosed diabetes For various reasons 302 clinistix positive persons failed to attend glucose tolerance tests and therefore several cases of previously undiagnosed diabetes may exist in the latter group Among the 854 examined persons there were 239 with so-called renal diabetes In the group of renal diabetes have been placed not only those who had fasting glycosuria but also those who got glycosuria during

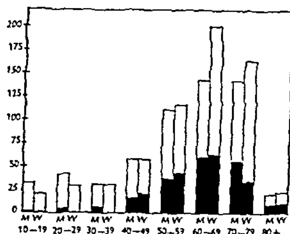


Fig 1 Age and sex distribution in 1,218 diabetics, both known (□) and new (■) cases in the population tested

TABLE II The diabetes duration (duration unknown in 1 woman and 7 men)

Years	♂	♀	Total
0–5	180	216	396
6–10	85	126	211
11–15	50	66	116
16–20	29	24	53
>20	31	31	62

1,156 persons glycosuria was discovered They had had no knowledge of this fact before the examination These 1,156 persons with positive clinistix reaction received notice to present themselves at the medical clinics in Karlskrona and Karlshamn for closer examination regarding the sugar level in the morning urine, the fasting blood sugar and, when necessary, the glucose tolerance 854 persons of those called in attended this examination Several of the remaining 302 persons with positive clinistix tests consulted their own physicians or went to the polyclinics of the hospitals, but as no glucose-tolerance tests were performed on these persons, these cases must be classed as uncertain

Diabetics

Altogether 1,218 diabetics were seen among the 97,862 persons examined, a frequency of 12 4 per thousand 372 of these diabetics were new cases i e previously undiagnosed and not under medical supervision for diabetes These new diabetics formed hardly one-third of the total number and represent a frequency of 3 8 per thousand of the population tested The remaining 846 cases were previously known diabetics, who were already being treated Fig 1 shows the age and sex distribution among the 1,218 diabetics The women outnumbered the men in ratio of 640 to 578 and were predominant in the age groups 50—69 years Most of the diabetics — almost three-quarters of the total number — were to be found within the 30-year age range from 50 to 79 years

Known diabetics

There are 846 known diabetics in the group The frequency of known diabetes was 8 6 per thousand in the group tested In most of the persons of this group the diabetes disease had made its first appearance after the age of 40 The duration of the disease is stated in table II

New diabetics

There were 372 previously undiagnosed cases in the group or 3 8 per thousand among those tested In fig 1 the black areas represent these cases 176 of these were women and 196 men 115 of the 372 new cases were diagnosed on the results of the fasting blood sugar values

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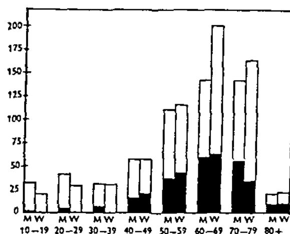


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where diabetes has a more dramatic start and where an early diagnosis is the rule

Discussion

The prevalence of diabetes mellitus in the tested population exceeds by far the figures previously reported after diabetes enumerations here in Sweden At the latest diabetes enumeration in Sweden, carried out by Silwer (20a) in the county of Kristianstad in 1954, the diabetes frequency was estimated at 5 1 per thousand In the examination that has been reported on here and that included 97 862 persons over 10 years of age tested with clinistix, the frequency figure was 12 4 per thousand — 11 7 for men and 13 2 for women If account is also taken of those 302 persons who did not present themselves for a complete examination and if we presume that the frequency of undiagnosed diabetes is as high as in the examined group of 854 persons the diabetes frequency in the population tested would be 13 8 per thousand

These figures show the same tendency as previously published results from mass surveys in the U S A (23) Canada (11) and Europe (10 19a) Yet the results shown by the examination in the county of Blekinge must be regarded as minimum figures

In every mass survey the technical methods employed and the diagnostic criteria chosen govern the number of diabetics detected If lower diagnostic blood sugar levels are set the number of diabetics detected will be larger This point of view together with other variable factors must be remembered when attempts are made to compare the results of the many mass surveys and the detection drives that are now being published Regarding the technique, the following factors which can influence the results can be stated 1 the screening method — urine analysis or blood sugar determination or both, 2 the blood sugar method — true glucose determination or total reducing substance, 3 the origin of the blood specimen — venous or capillary blood, 4 the time of examination in relation to meal — fasting or postprandial, 5 the diagnostic criteria of diabetes 6 the type of glucose tolerance test and the evaluation of the results 7 the relative success in the follow up of all tho e with initially abnormal results so that diagnosis can be made in each case From the aspect of the tested population certain other viewpoints arise It is important for example, to know the age and sex distribution and the selection method if any, in those tested among the whole group Perusal of the literature on mass surveys and case finding programmes for the detection of previously unknown diabetes shows that blood analysis generally gives 0 5 to 1 % new diabetics and mere urine analysis less than 0 5 % (8 10 17) As the urine specimens in the present investigation were taken after a meal and as clini tix was used for the analysis of the urine specimens it is unlikely that many latent diabetics were missed Yet it must be fully realized that there are many latent diabetics with a high renal treshold especially in the advanced age groups It has not of course been possible to diagnose these cases by means of urine sugar analysis

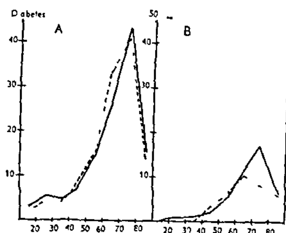


Fig 2 The frequency of diabetes in the population tested (97,862 cases) in relation to age and sex
A The frequency of diabetes (new and known) in the population tested B The frequency of previously undiagnosed diabetes in the population tested
Men ———— Women — — — —

the glucose-tolerance tests without the peak of the curve rising above 180 mg/100 ml

The frequency of diabetes within each age group

The total number of diabetics in the tested population of 97,862 persons was 1,218 372 of this number were new diabetics and 846 known diabetics Fig 2 shows two pairs of curves, the first pair showing the total frequency of diabetes within each age group of the population tested, the second pair showing the frequency of only previously undiagnosed diabetes in the population tested It can be seen from the curves that the diabetes frequency for men in the age group 10—19 years is somewhat higher than for women and is 3 2 per thousand and 2 1 per thousand respectively In the age groups 20—29 years the same fact can be seen, the diabetes frequency here being 5 6 per thousand for men and 4 2 per thousand for women In the age group 30—39 years the diabetes frequency is the same for both sexes In the age groups 50—59 and 60—69 women are predominant with 15 3 per thousand and 33 2 per thousand respectively compared with 14 2 per thousand and 25 7 per thousand respectively for men In the age groups over 70 years the frequency of diabetes is almost the same, only a slight predominance for men In the age group 70—79 years we came across the largest number of diabetics with a frequency of 41,5 per thousand for women and 43,1 per thousand for men

When tracing new cases the greatest success was achieved when testing the women between 60 and 69 years and the men between 70 and 79 years, the new diabetics being 10 4 and 17 per thousand respectively These curves serve to draw attention to that part of the public with the highest incidence of diabetes As is apparent from the tables and from the above mentioned facts, diabetes is a disease which chiefly affects people beyond the age of 40 years From an epidemiological point of view this is an observation of the greatest importance, as any project with the aim of getting hold of the greatest possible number of known and unknown diabetics, must concentrate on the older generation Furthermore, in this group the diabetes disease can remain undetected for long periods of time and complications can develop and progress before a diagnosis is made This is contrary to the situation in the young age groups

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Harting and Glenn (8) made a comparison between urine-sugar and blood-sugar determinations as screening tests and showed that the latter are superior in the discovery of mild cases of diabetes Enzyme tests are more sensitive than the copper-reduction methods for detecting glycosuria (3, 5, 20) In order to enhance the value of the urine analysis as a screening method, many authors suggest that the urine should be examined after a meal rich in carbohydrates (1, 6)

This mass survey in the county of Blekinge is the largest examination of the prevalence of latent diabetes that has been carried out in Europe before 1961 It gave us important information about the frequency of diabetes in a large population and, besides, it revealed many cases of latent diabetes Most of those cases were people of middle-age and older The investigation clearly proves that there is a fairly large group of latent diabetes cases in the population It would therefore be very expedient for all persons over the age of 40 to have a urine test at least once a year This may lead to earlier discovery and treatment Most authors embrace Naunyn's old thesis that the prognosis is best when the disease is early diagnosed and thoroughly treated The results of this survey, although preliminary, can also be used as a basis for an estimation of the number of diabetics in the whole of Sweden The incidence of diabetes can then probably be estimated at 90,000—100,000

Summary

Data concerning the prevalence of diabetes mellitus in the county of Blekinge, Sweden, are presented A total of 97,862 persons were tested for diabetes In the survey 80 per cent of persons over the age of ten were included Postprandial urine samples were used as screening material and were tested for glucose by the clinistix method 1,218 diabetics (12,4 per thousand of the population tested) were encountered 372 (3 8 per thousand) were previously undiagnosed and 846 (8,6 per thousand) were known diabetics, In certain age groups — women from 66 to 79 years and men from 70 to 79 years — over 10 per thousand of those tested were diabetic Glycosuria of both diabetic and non diabetic origin occurred in 16 per thousand of 97 862 persons examined

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The Radiological Diagnosis of Non-specific Haemorrhagic Proctocolitis (Haemorrhagic Proctitis and Ulcerative Colitis)

By

INGER KINSEY NICOLAY HORNNES, POUL ANTHONISEN and POVL RIIS

The radiological findings in non specific haemorrhagic proctocolitis (haemorrhagic proctitis and ulcerative colitis) were first described in 1912 by Stierlin (3) Since then much has been published on the subject, but nevertheless the radiological diagnosis has been beset with uncertainty except in cases of proctocolitis in the more advanced stages showing ulcerations, pseudopolyposis etc

The first aim of this paper is to describe the radiological findings in a series of proctocolitis cases of all degrees of severity Cases of very slight activity have been included and non inflammatory colon diseases with similar symptoms excluded This has been made possible by use of the cytological examination of the secretion from the rectosigmoidal mucosa which has been described elsewhere (1)

Secondly it is sought to assess how far the radiological changes discovered are specific for the disease

Submitted for publication January 15 1964

Material and methods

The primary material consists of 54 X ray examinations of 50 proctocolitis patients (38 women and 12 men with ages from 14 to 78 years average 38 years) The patients were examined and treated at the Glostrup Hospital during the period 1st January 1960 to 1st June 1963 The diagnosis was determined by anamnestic and proctoscopic criteria usually employed but also in the great majority of cases the diagnosis has been confirmed by use of the cytological examination mentioned above (1) The cytological method has had a decisive importance in the diagnosis of the milder cases of proctocolitis

In the X ray examinations the double contrast technique according to Welin (4) has been used

About 350 colon examinations according to Welin (recovery material), carried out at Glostrup Hospital in the period 1st January 1960 to 1st June 1963 have been reviewed in order to estimate the specificity of the radiological findings These examinations were performed mainly on patients with symptoms of colon disease and in a minor group for the purpose of tracing occult cancer

Among the 350 examinations there were 45 cases in which the proctocolitis diagnosis

TABLE I Fifty four examinations of the colon (according to Welin) of 50 patients with non specific proctocolitis (haemorrhagic proctitis and ulcerative colitis)

Pathological findings	Examinations	Percentage (of 48 examin)
Granulated contrast surface	42	88
Spicule formation	40	83
Ulceration	20	42
Spasms and dehaustrations with varying localisations	9	19
Fixed stenoses and dehaustrations	8	17
Normal findings	5	10
Increased presacral space	4	8
Polyps	3	6
Pseudopolyposis	3	6
Ileum included in the inflammatory process	1	2
Technically unsatisfactory	6	

was called for if the criterion were the presence of one or more of the three most frequent *radiological findings in the primary material* of 54 proctocolitis examinations The X ray diagnoses were afterwards compared with the *clinical diagnoses of the patients concerned*

The appraisals of all the X ray examinations were made by two of the authors (I K *and* Y *H*) *who in general had no knowl*edge of the clinical diagnoses The clinical diagnoses were given by the two other authors (P R and P A) on criteria other than the radiological findings

Results

Table I sets out in order of frequency the radiological findings in 54 colon examinations (Welin s procedure) of 50 proctocolitis patients who formed the primary material Six technically unsatisfactory examinations (of 6 patients) are not included in the percentages given In 5 examinations (of 4 patients) the colon was found to be normal radiologically In most cases the remaining examinations showed several different findings present at the same time

The classification 'granulated contrast surface' may be difficult to judge as there are many gradations from the normal mucosa on which the contrast is seen as a uniform veil (fig 1a) to the typical granulation where numerous small contrast particles are spread over the mucous membrane (fig 1b—d)

Spicule formations" are more easily determined as the fine pin point like spikes show up clearly on the sharp contour of the colon wall (fig 1c), or, as is frequently seen, on a contour having a slightly irregular edge (fig 1d) Where spicule formations were observed only on pictures of the contrast filled colon but not after air insufflation, the cases have not been included in the above table Such spicules are found fairly frequently *in patients with diagnoses* other than protocolitis

From spicule formation' to ulceration is an easy transition Ulceration here includes all defects from pinhead sized to deep niches (fig 1e)

Only fixed stenoses and dehaustrations can be taken as signs of inflammation or its sequelae as it is well known that alternating spasms and dehaustrations *are frequently found in functional* colonic diseases

Pseudopolyposis may be difficult to distinguish radiologically *from familial* polyposis but a differential diagnosis here where a group of proctocolitis patients is concerned can hardly be said to be relevant

a

b

c

d



e

Fig. 1. Double contrast examinations according to Welin. a) normal person; b—e proctocolitis patients. a Normal contrast surface and contour. b Fine granulated contrast surface. c Spicule formation and granulated contrast surface. d Granulated contrast surface as well as spicule formation with slightly irregular contour line. e Ulcerations (x) filled with contrast: to the right; to the left the picture after air insufflation.



Fig 2 Severe changes (ulceration pseudopolyposis etc) in the left half of colon accumulation of faecal masses in the relatively normal right half of colon

The accumulation of faecal masses in a fairly normal right half of the colon together with severe pathological changes in the left half of the colon has been observed earlier (2), and has been noticed in several examinations in the present series (fig 2) As the radiological changes in the lower half of the colon are always very pronounced in such cases reference to the faecal accumulation in the right half of the colon has not been included in the table

The phenomenon toxic megacolon (pronounced dilatation of one or more colon segments in patients with severe fulminating proctocolitis, often the forerunner of perforation) is not included in the table The table is based on radiological examinations following Welin s technique, a technique not used in cases of exhausted or intoxicated patients The radiological diagnosis ' toxic megacolon is made on the plain film

The only patient in the series with changes in the ileum, as well as in the colon, was a 17 year old girl

As stated, among about 350 Welin examinations (recovery material) undertaken in the period during which the primary material was collected there were found 45 in which the proctocolitis diagnosis must be made, the criterion being the presence of one or more of the three first findings set out in table I It emerged then that 43 of these examinations were of patients with clinical proctocolitis, and thus of patients included in the primary material Only two examinations were of patients whose clinical diagnoses were other than non specific proctocolitis These two patients case records are referred to briefly

1 A 61 year old man who had been for 11 years a missionary in Africa and who had suffered from chronic amoebic dysentery At the time of the examination there was no diarrhoea but there were symptoms of an irritable colon The cytological examination showed inflammation without eosinophil a amoebae were not demonstrated

The probable diagnosis for this patient is amoebic dysentery or its sequelae

2 A 61 year old woman with chronic constipation from childhood From time to time blood streaks had been observed on the faeces Other symptoms appearing were suggestive of irritable colon Following an enema during the admission there was bleeding from the rectum Cytological examination some days afterwards showed inflammation without marked eosinophilia in all later examinations in the course of more than a year the cytologic analyses have shown wholly normal conditions No diverticula were demonstrated in the colon

An irritable colon is the most likely diagnosis, the inflammation discovered on one occasion could be due to an artificial lesion

Discussion

Inflammation in the mucous membrane of the colon naturally cannot be ascertained by radiological examination, and strictly speaking the diagnosis proctocolitis cannot be arrived at on the basis of the X ray picture alone Yet, radiological examination of the colon must be able to help in the differential diagnosis if certain changes are found sufficiently frequently in the disease and assuming that these changes are not found or are only rarely found, with other diseases of differential diagnostic relevance The laying down of diagnostic criteria will, of course, indirectly have a bearing on the utility of radiological examination as a measure of the extent of the affected area

Granulated contrast surface and spicule formation were found in the majority of the present group of patients with clinically verified non specific *proctocolitis* Ulceration was a somewhat *rarer discovery* this is a *consequence* of the inclusion in the material of cases *of all* degrees of severity

Spasms and dehaustrations with varying localisations were found quite frequently These findings cannot now be used as criteria of *proctocolitis* because as is well known they occur very often among patients with functional colonic diseases such as chronic *constipation* and irritable colon Consequently the finding of alternating spasms and *dehaustrations* does not justify diagnoses that suggest inflammation as a cause (i e proctocolitis or likewise, for example 'mucous colitis', spastic colitis" etc)

Fixed stenoses and dehaustrations may well reflect present inflammation in the mucosa, but may also be due to previous processes of an inflammatory or other nature This finding is also unsuitable as a criterion for proctocolitis

Increased presacral space polyps and pseudopolyposis were so seldom found in the present investigation that these findings cannot have any great significance for the radiological diagnosis of proctocolitis

It has been asserted (5) that only the discovery of ulceration would give adequate support for the diagnosis of *proctocolitis* In the current work ulceration was found *only in* about $2/5^{ths}$ of the examinations of proctocolitis *patients* (primary material), and *if in the latter* part *of this* work (recovery material) this radiological finding had been used as the only criterion there *would have* been *found* only a small minority *of the proctocolitis* cases Moreover, there still *would have been* a wrong appraisal of *one of* the two patients who did not have clinical *proctocolitis* (case 2) as this patient had pronounced ulceration in the radiological examination

One or more of the radiological findings granulated contrast surface spicule formation and ulceration were found in *about* $9/10^{ths}$ of the proctocolitis patients *examined* (primary material) and in the *recovery material* the presence of one or *more of these* findings being used as *criterion* almost all the proctocolitis *cases* were tracked down Since moreover, in

the recovery material only two patients without clinical proctocolitis fulfilled this criterion, the conclusion of the present examination must be that the presence of one or more of the radiological findings granulated contrast surface, spicule formation and ulceration gives excellent support to the diagnosis non-specific proctocolitis At least this holds good in Denmark, it must be stressed that nothing set out above holds for differential diagnosis concerning the common types of acute enteritis in this country, for which radiological examinations according to Welin are usually not undertaken, nor again concerning exotic intestinal infections of which only a single doubtful case is included in the examination series (amoebic dysentery)

Summary

Non-specific haemorrhagic proctocolitis is a disease of an inflammatory nature Inflammation in the mucous membrane of the colon cannot be established by radiological examination, but certain findings can support the proctocolitis diagnosis if they are found sufficiently frequently in patients with the disease, but not at all or only rarely in other diseases of differential diagnostic relevance

Among 50 patients with clinically verified non specific proctocolitis of all degrees of severity, 54 radiological examinations according to Welin were carried out ("primary material") Six examinations (of six patients) were unsatisfactory, five examinations (of four patients) showed normal conditions The three most frequent pathological findings were granulated contrast surface, spicule formation and ulceration That ulceration was found comparatively rarely in the present material is undoubtedly due to its composition of cases of all degrees of severity

Among about 350 Welin examinations ("recovery material") undertaken in parallel with collection of the primary material, there were found 45 which called for the radiological diagnosis proctocolitis by the criterion of the presence of one or more of the three most frequent radiological findings in the primary material Forty-three of the examinations were on patients with clinically verified proctocolitis, whilst one was on a patient with assumed chronic amoebic dysentery and one on a patient who probably had an irritable colon

Consequently the presence of one or more of the radiological findings granulated contrast surface, spicule formation and ulceration strongly supports the clinical diagnosis non-specific haemorrhagic proctocolitis, at least in Denmark where the differential diagnosis concerning acute enteritis is seldom of current interest and where chronic intestinal infections of the more exotic types as yet appear only sporadically

Acknowledgement

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Hypercalcaemia in Renal Carcinoma

Report of a Case

By

B A Lamberg, R Pelkonen and M H Frick

The association of hypercalcaemia with malignant tumours has long been known and was formerly usually attributed to osteolytic metastases to the bone (3) In several cases this explanation has not been tenable however and other possible mechanisms have been proposed (28 31) Hypercalcaemia without bone involvement has been reported in carcinoma of the lung the ovary the kidney and in addition in single cases of tumours arising in other tissues (19 30) Furthermore Gordan et al (15) mention several cases of hypercalcaemia in patients with breast cancer of long duration without evidence of bone metastases Hypercalcaemia associated with renal carcinoma without apparent bone *metastases has been reported in 9 in*stances 1 7 10 11 28) The present report concerns a case of renal carcinoma with one metastasis to the bone but with unusually pronounced bone changes regarded as typical of hyperparathyroidism

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Case report

The patient a male aged 42 started to complain of colicky pains in the mid back region in the summer of 1962 The pains appeared at varying *intervals and slight* haematuria was observed which aroused a suspicion of renal calculi In autumn 1962 he commenced to have low grade fever constipation and at times severe pain in the upper abdomen His appetite remained unchanged but he felt thirsty and there was a weight loss of 6 kg in 3 months

He was admitted to the hospital in December 1962 His constitution was asthenic the skin normal except for pallor and the general condition was good On palpation a mass in the left hypogastrium was vaguely *felt* Small lymph nodes were present *in* the groins

Laboratory examinations Hb 8 1 g/100 ml RBC 3 26 mill /mm^3 WBC 9 000/mm^3 with a normal differentiation The bone marrow aspirate was normal Serum iron 28 μg/100 ml the ESR (Westergren) 120 mm/hr Paper electrophoresis of the serum proteins showed elevation of alpha$_2$ globulins. There was no glucosuria or proteinuria the specific gravity of the urine varied from 1 003 to 1 008 and in the sediment 10—15 *red cells*

the recovery material only two patients without clinical proctocolitis fulfilled this criterion, the conclusion of the present examination must be that the presence of one or more of the radiological findings granulated contrast surface, spicule formation and ulceration gives excellent support to the diagnosis non-specific proctocolitis At least this holds good in Denmark, it must be stressed that nothing set out above holds for differential diagnosis concerning the common types of acute enteritis in this country, for which radiological examinations according to Welin are usually not undertaken, nor again concerning exotic intestinal infections of which only a single doubtful case is included in the examination series (amoebic dysentery)

Summary

Non-specific haemorrhagic proctocolitis is a disease of an inflammatory nature Inflammation in the mucous membrane of the colon cannot be established by radiological examination, but certain findings can support the proctocolitis diagnosis if they are found sufficiently frequently in patients with the disease, but not at all or only rarely in other diseases of differential diagnostic relevance

Among 50 patients with clinically verified non specific proctocolitis of all degrees of severity, 54 radiological examinations according to Welin were carried out ("primary material") Six examinations (of six patients) were unsatisfactory, five examinations (of four patients) showed normal conditions The three most frequent pathological findings were granulated contrast surface spicule formation and ulceration That ulceration was found comparatively rarely in the present material is undoubtedly due to its composition of cases of all degrees of severity

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Fig 2 Granular decalcification and moth-eaten appearance of the skull bones

ination of the parathyroids revealed a perfectly normal structure The operation had no effect whatever on the serum calcium and phosphorus (table I) After the operation the general condition of the patient deteriorated rapidly There was further loss of weight the patient experienced severe colicky pains in the abdomen polyuria and polydipsia and the constipation was further exaggerated He was transferred to the Medical Department after which hemiplegia developed on the left side

At this time the patient appeared rather cachectic and rapidly went into a state of dehydration with marked polydipsia and polyuria A hard nodular mass was now readily palpated in the left lower abdomen

In the third right rib a small hard nodule the size of a thumb-tip was palpated

Laboratory examinations Hb 11 [illegible] g 100 ml serum iron 45 µg 100 ml total iron binding capacity 124 µg 100 ml haematocrit 34 % WBC 8 300 mm³ ESR 124 mm 1 hr Plasma proteins 6 3 g 100 ml and paper electrophoresis [illegible] revealed elevation of the alpha₂ globulins 1 4 g 100 ml On immunoelectrophoresis the presence of an abnormal protein at the location of the beta-globulin was observed [illegible] LDH [illegible] 000 units ml [illegible] serum Serum creatinine 0 [illegible] 1 3 mg 100 ml sodium 138 145 mEq l chloride 95 [illegible] mEq l pH of the capillary blood [illegible] 45 pCO₂ 40 4 mm Hg No glu

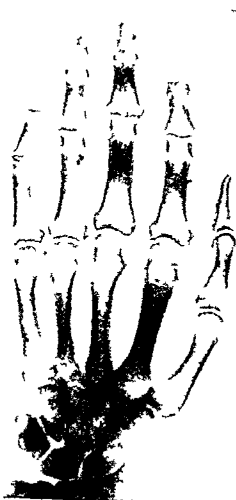


Fig 3 Cyst like lesions and subperiosteal resorption of bone in the finger bones

cose or protein was found in the urine the specific gr of the urine varied from 1 00? to 1 006 The urinary sediment contained 1—3 red cells and 30—35 white cells per high power field Data on calcium and phosphorus are given in table I The administration of prednisone 40 mg a day for 17 days had no effect on the calcium in the blood and the urine The ECG showed changes typical of hypercalcaemia with short Q T intervals and absence of S-T segments (fig 1)

Histological examination of the biopsy specimen taken from the nodule in the rib

TABLE I Some laboratory data concerned with the metabolism of calcium

	Before Dec 1962—Jan 1963	After op Feb 1963	Final admission March—April 1963
Serum Ca (mg/100 ml)	12 7—13 6	12 7—14 6	14 0—17 0
Serum P (mg/100 ml)	2 6— 3 4	1 7— 4 0	3 0— 3 7
Alkaline phosphatase (King Armstrong U)	37 5	20 6—35 8	13 4—17 8
Urinary Ca (mg/24 hrs)[1]	252— 587	149— 592	277—313
Urinary P (mg/24 hrs)[1]	439—1 036	379—1,394	713—990
Tubular reabsorbtion of phosphate (%)[1]	72	53— 66	—

[1] On ordinary hospital diet

were seen per high power field Culture of the urine gave a growth of *Diplococcus pneumoniae* Data on calcium and phosphorus are listed in table I *Radiological examinations* In the upper lobe of the right lung there was a small (about 1 sq cm) round infiltration On intravenous cholecystography the main bile duct appeared normal but the gallbladder was not visualized An X-ray picture of the stomach revealed nothing abnormal Intravenous pyelography there was a small calcification in the right kidney which was larger than the left one and the upper calyces appeared clubbed Radiographs of the bones the long bones showed a coarse trabeculation and there was an apparent subperiosteal bone resorption in the diaphyses of the finger bones

Since there was evidence of primary hyperparathyroidism but the possibility of renal carcinoma of the right kidney, conceivably causing the hypercalcaemia could not be ruled out, the patient was transferred to the Second Surgical Department (Head Prof Vaino Seiro M D) for exploration of the neck region This was performed on January 18 1963 but in spite of a careful search no parathyroid adenoma could be found in the neck or the mediastinum At the operation subtotal thyroidectomy was performed the thymus was removed and in addition two parathyroid glands Microscopical exam

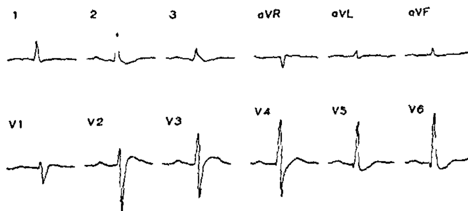


Fig 1 Electrocardiogram showing shortening of the Q—T intervals and absence of S T segments typical of hypercalcaemia

ever there is an increased osteoblastic activity of the bone Hence, it may be elevated in malignant disease with or without metastases to the bone (3, 16) Furthermore, it is elevated only in a certain proportion of cases with hyper parathyroidism (13, 22)

4) Treatment with cortisone, originally stated not to affect the hypercalcaemia of hyperparathyroidism (12), has more recently been observed not to be an unequivocal test of increased parathyroid function Several exceptions to the original pattern have been reported A decrease in the serum calcium level has occasionally been observed in primary hyperparathyroidism (15, 17, and one unpublished personal case) On the other hand cortisone treatment does not always depress the serum calcium level in cases of hypercalcaemia due to other causes for instance in malignant disease (9 32) In an extensive review of the regulation of serum calcium, Myers (26) has expressed the view that in principle, cortisone should depress the serum calcium level even in hyperparathyroidism through some action on the extracellular fluid bone calcium homeostatic mechanism The reaction may then depend on several factors including the length of treatment and the dosage used

In the present case several features were suggestive of primary hyperparathyroidism low serum phosphate low TRP elevated alkaline phosphatase and unresponsiveness to prednisone Furthermore the finding of cystic lesions and considerable subperiosteal bone resorption in the phalanges of the fingers and the moth eaten appearance of the calvaria in X ray pictures supported this view Although subperiosteal resorption of bone may also occur in other conditions (19) such pronounced changes as were seen in this case would rather indicate a parathyroid hormone like action on the bone In hypercalcaemia with malignant disease without bone metastases histological evidence for increased bone resorption has been found in some cases (31) but not in all (28) and the radiological findings have usually been normal, in only one case was a local erosion seen (31)

The possibility of primary hyperparathyroidism was considerably lessened, although not excluded, by the negative findings on surgical exploration and later on, at autopsy It remains obscure why only two parathyroid glands were found but if the other two glands were located within the thyroid they might have been removed with the thyroid tissue at thyroidectomy In spite of the removal of at least two glands there was no change in the level of the serum calcium

From the start the patient exhibited some unusual features not primarily compatible with primary hyperparathyroidism a profoundly elevated ESR elevated $alpha_2$ globulins and furthermore a mass in the hypogastrium, abnormal renal findings pulmonary infiltrations suggestive of metastatic malignancy probably a renal carcinoma This was also later confirmed by biopsy and at autopsy The finding of a malignant metastasis in one rib might suggest that the hypercalcaemia was primarily due to this metastasis That it need not necessarily be so is illustrated by the original observation of Albright

revealed malignant growth of cells with a large clear cytoplasm suggestive of clear cell renal carcinoma

X ray examinations Numerous round infiltrations were seen in both lungs The skull showed granular decalcification (fig 2) Small cyst like lesions were present in the middle phalanges of the fingers and the subperiosteal bone resorption in these bones was now more apparent than on the first occasion (fig 3)

The patient succumbed 5 weeks after admission *Autopsy report* In the left ventricle of the heart a recent myocardial infarction was found and the coronary arteries revealed marked atheromatous changes The right kidney was throughout infiltrated by light-coloured tumour nodes the size of a finger tip *Histological examination* showed growth of undifferentiated malignant tissue with large cells, the cytoplasm of which contained abundant pale lipid characteristic of clear cell renal carcinoma Soft tissue metastases were found in the right parietal lobe of the brain in the left kidney, in both lungs, in the liver and along the mesenteries of the small and large bowel

The only bone metastasis found was that in the rib The entire spine was cleft but no metastases were discovered Nor were any metastases observed in the skull

In spite of a very careful search no parathyroid tissue was found either in the thoracic cavity or in the neck

Discussion

In the evaluation of the calcium metabolism of the present case several points had to be considered Many of the causes for hypercalcaemia could be excluded initially and there remained three major possibilities 1) hypercalcaemia due to bone metastases, 2) hypercalcaemia of malignant tumour without metastases to the bone, and, 3) primary hyperparathyroidism coincident with malignant tumour After one metastasis in the rib had been revealed item 2) could be excluded from the list The reasons that this possibility is still given some consideration will be explained below

The behaviour of the serum phosphate, the tubular reabsorption of phosphate (TRP), the serum alkaline phosphatase and the response to cortisone (prednisone) treatment do not provide an unequivocal basis for the differential diagnosis, for the following reasons

1) The significance of the serum phosphorus level is difficult to assess (22) It largely depends on what is accepted as the lower normal limit Although usually normal or elevated in malignant disease (3, 15) it has occasionally been found to be low (3) In cases with malignant disease without bone metastases it has usually varied from about 1 7 to about 5 0 mg/100 ml, a considerable proportion of cases, however, exhibiting values below 3 5 mg/100 ml (*e g* ref 30)

2) A decrease of TRP originally regarded as characteristic of primary hyperparathyroidism has also been observed in other conditions with hypercalcaemia, and, on the other hand, normal values have been observed in hyperparathyroidism (15, 29) Since TRP is largely dependent on the phosphate load filtered, and, hence, on the phosphorus intake the appraisal of a single value when the diet has not been standardized is difficult (15 29) It has also been found to be low in a few cases of hypercalcaemia with malignant disease without bone metastases, and normal in some instances (e g ref 30)

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and Reifenstein (2) In their case hypercalcaemia was associated with a single metastasis located in the pelvic girdle and probably of renal origin Irradiation of the metastasis induced a fall in the serum calcium level and the possibility that the tumour may have produced a substance with parathyroid hormone-like action was considered These authors held the view that the serum calcium level was disproportionately high in view of the presence of only a single bone metastasis A similar reasoning may be applicable to the present case Furthermore, the patient had had a renal calculus already one year previously and on the first roentgenological examination 2 months before the rib metastasis was found, there were no indications of a metastasis in the ribs

It is also of interest to observe that apart from the increase in alpha $_2$-globulin not uncommon in renal carcinoma immunoelectrophoresis revealed the presence of an abnormal protein at the site of the beta$_1$-A-globulin, since abnormalities in this particular region have been observed in primary hyperparathyroidism (2)

In view of the above considerations the authors are of the opinion that the hypercalcaemia in the present case was probably secondary to the renal carcinoma, not by way of bone metastases but by the mediation of some other mechanism Several hypotheses have been proposed in order to explain the pathogenesis of hypercalcaemia with malignant disease without bone metastases (28, 30, 31) The following possibilities have been considered The tumour may produce a substance 1) with a parathyroid hormone like action 2) with parathyroid stimulating properties, 3) with a vitamin D like action or 4) it may produce some substances which by unknown mechanisms are able to alter the extracellular compartment — bone calcium homeostasis There is, however, no unequivocal evidence for any of these possibilities (19) and it has also been considered unlikely that the wide variety of different types of malignant tissue in association with which hypercalcaemia has been reported to occur could elaborate a parathyroid hormone like substance (26) On the other hand, it is also possible that several different mechanisms are at work

Parathyroid hormone like activity has not been detected on direct assay of the tumour tissue in those few instances in which such an assay has been carried out (5, 7) On the other hand, the possibility that some malignant tumours actually produce a substance with such an action cannot be totally rejected A variety of endocrine disturbances have been described in association with malignant tumours (33), the commonest of which seems to be hyperadrenocorticism (21, 25) In some instances an ACTH-like activity has been noted in the blood (4, 8, 23) and on direct assay, in the tumour tissue, in patients with Cushing's syndrome with malignant disease (14, 18, 23, 25) Recently TSH like activity has also been found in malignant tumour (27) It may be recalled that hypercalcaemia can be induced in rabbits by the XV 2 carcinoma (34)

The parathyroid glands have usually

been normal in these cases of hypercalcaemia without bone changes Some evidence of stimulation has been observed in two instances (6, 31)

Gordan et al (15), in studies on breast cancer, observed 20 cases with hypercalcaemia without bone metastases They showed that osteolytic changes could be produced by breast cancer tissue, parathyroid tissue and vitamin D when implanted against the *calvaria* of the rat These authors are of the opinion that the osteolytic substance in patients with breast cancer is more like vitamin D than like parathyroid hormone No cortical erosions were observed in their cases whereas such are found in about 20 per cent of cases with primary hyperparathyroidism

In addition to the production of substances with specific hormone or vitamin like action on the bone, the possibility of the formation of some other material which may directly or indirectly induce changes in the homeostatic regulation of the serum calcium by unknown mechanisms has been speculated upon (26) There is no real evidence in favour of this view but the finding of a calcium complexing substance in the serum of patients with hypercalcaemia (24) may have some bearing on the problem (19)

In the present case a parathyroid hormone like action on the bone could not have been mediated by the parathyroid glands since the two glands found were entirely normal Hence the action on the bone must have been induced by some other substance In view of the very marked bone changes observed on radiological examination this substance more probably had a parathyroid hormone like activity than a vitamin D like effect but whether this effect was induced directly or indirectly by some substance formed by the carcinoma tissue remains, of course, quite obscure

Summary

A case of hypercalcaemia in association with renal carcinoma is presented A single bone metastasis was detected in one rib In addition to hypercalcaemia a low serum phosphorus level, decreased tubular reabsorption of phosphate and unresponsiveness of the serum calcium level to treatment with prednisone was observed Cystic lesions and considerable subperiosteal bone resorption in the phalanges of the fingers was found on radiological examination and the *calvaria* of the skull had a moth eaten appearance The above changes were considered not to be due to bone metastases but rather to the presence of some substance probably having a parathyroid hormone like activity Two parathyroid glands were normal on histological examination, the other two were not found either at operation or at autopsy They may have been removed at thyroidectomy

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Congenital Heart Disease in a Clinical Material

An Analysis of 1,000 Consecutive Cases

By

OLE STORSTEIN ROLF ROKSETH and SVEIN SORLAND

The incidence of the various forms of congenital heart disease is different in clinical and autopsy materials The more severe and complicated forms will be seen more often at autopsy, while clinical material will comprise cases with a somewhat better prognosis as it consists of patients referred to hospital for investigation prior to surgery The various clinical materials will also show a changing trend from time to time Those collected 10 to 15 years ago mainly consisted of cases amenable to surgery at that time patent ductus arteriosus coarctation of the aorta Fallot s tetralogy With the progress in cardiac surgery and anesthesia other forms of congenital heart disease are now referred for study and studies of later years will show an increasing percentage of cases of atrial septal defect and ventricular septal defect Thus the various statistics of congenital heart disease presented from cases collected at autopsy or by clinical study do not represent the true incidence of congenital heart disease in a population

With this drawback in mind we are going to present the first 1,000 patients studied at the Cardiological Laboratory, Rikshospitalet, University of Oslo

Material

The cases have been collected from March 15 1959 when the Cardiological Laboratory opened until December 7, 1962 Among these 1 000 patients cardiac catheterization has been carried out at this laboratory in 595 patients Fifty two patients have been catheterized in other laboratories In the remaining 353 patients the diagnosis has been made on clinical grounds The main groups in the cases studied only clinically are patent ductus arteriosus and coarctation of the aorta.

In the classification of the material we have followed Wood s classification dividing the patients into those without shunt and those with shunt The former group again is divided into general faults leftsided and rightsided anomalies The cases with shunt are divided into acyanotic and cyanotic cases In table I the material is presented

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TABLE I Percentage distribution of diagnostic groups in 9 materials of congenital heart disease The open spaces in some of the series signify that the diagnosis is not mentioned specifically in the statistics of these materials and difficult to determine from the text

	Abbott (1) (postmortem material)	Gasul & Fell (3) (90% < 16 years)	Keith et al (5) (0—15 years)	Wood (9) (all ages)	Kjellberg et al (6) (predominately children)	Hansen & Warburg (4) (92% > 5 years)	Burgemeister (2) (3—14 years)	Nadas (7) (mostly children)	Storstein et al (10 years)
No of patients	1000	1395	1866	900	742	1678	794	3786	1000
No shunt									
General									
Dextrocardia	2 9	1 7		0 5		0 2	0 6		*0 6
Levocardia		0 5							*0 1
Heart block	0 3			1 5					0 7
Pericardial defect	3 0								0 1
Left sided									
Aortic atresia	1 2		2 0					ca 0 3	
Aortic hypoplasia	0 2			0 5				ca 2 0	0 1
Aortic incompetence (isolated)				0 5		}3 6			0 5
Aortic stenosis	2 3	2 1	4 0	3 0	3 4		3 5	5 7	4 8
Coarctation of the aorta	8 5	5 5	6	9 0	13 8	7 2	2 8	5 0	4 7
Cor triatriatum	1 0		0 1?			0 1		0 1	
Fibroelastosis		1 5	1 0						0 2?
Mitral stenosis mitral atresia	1 1	1 6			1 2		0 5	0 2	0 1
Anomaly of coronary artery	1 5	0 5	0 5		0 3		0 1	0 1	*0 3
Right sided									
Ebstein s anomaly		0 5	<1 0	1 0	0 9	0 7	0 3	ca 0 4	0 2
Idiopathic dilatation of P A	0 6	1 2		1 0	0 7	1 4			0 5
Pulmonary stenosis (isolated)	0 9	2 9	7 0	12 0	11 3	10 4	4 8	12 0	0 9
Pulmonary incompetence (isolated)	0 2				0 3			ca 0 1	0 4
Idiopathic pulmonary hypertension		0 4			0 4			ca 0 1	1 1
With shunt									
Acyanotic (left right shunt)									
Patent ductus arteriosus	10 5	10 7	17 0	13 0	19 2	21 0	8 7	*12 3	12 9
Atrial septal defect	3 3	9 6	7 0	18 0	10 4	18 0	8 6	*14 0	19 1
Anom pulm venous drain (part)				?	*2 8		*0 4	ca 0 5	*2 2
Ventricular septal defect	5 5	20 5	22 0	8 0	10 3	6 5	22 7	ca *15 0	15 1
VSD with pulmonary stenosis	8 5	}3 0		1 3	1 7			ca 5 0	2 8
ASD with pulmonary stenosis				2 0	0 9	1 5			1 0

TABLE I (cont)

	Abbott (1) (postmortem material)	Casal & Fell (3) (90 < 16 years)	Keith et al (5) (0—15 years)	Wood (9) (all ages)	Kjellberg et al (6) (predominately children)	Hansen & Warburg (4) (94 % > 5 years)	Burgemeister (2) (3—14 years)	Nadas (7) (mostly children)	Storstein et al (50% ≦ 10 years)
No of patients	1000	1395	1866	900	742	1678	794	3786	1000
With shunt									
Cyanotic (right left shunt)									
Tricuspid atresia	1 6	1 7	3 0	1 5	1 9	0 5	1 5	1 2	0 3
An m drain of SVC/IVC to LA	0 9								0 3
Cor triloculare or biloculare	2 7	0 9	2 0		0 3		0 2		0 1
Fallot's tetralogy	11 5 (tetralogy and pentalogy)	11 1	11 0	11 0	8 6	14 3	19 7	*14 6	8 0
Fallot's pentalogy		0 6					2 0		0 5
Pulmonary atresia	1 4		1 0	1 7	0 3			0 1	0 2
P sten with R L interatr shunt				3 0		3 2	1 3		0 7
P hypertension with manifest or threatening R L shunt									
1 Patent ductus				2 0				*> (10 0) ? (items 1–5)	1 5
2 Aortic pulm sept defect	1 0	0 2		0 3					0 3
3 VSD (*Eisenmenger complex*)		1 8	3 0	3 0	4 6	2 9	3 2		5 3
4 ASD				1 5					1 3
5 Atrio-ventriculare commune*		2 3	2 0		0 9				0 4
Transposition of great vessels	4 9	4 6	8 0	1 0	2 7	0 7	1 6	4 0	1 8
Persistent truncus communis	2 1	1 7	<1 0		0 1		0 4	ca 0 5	0 1
Tot anom PV drain to SVC/RA	0 4	0 4	2 0				0 6	ca 0 8	0 2
Miscellaneous comb or undiagnosed	22 0	12 5	ca 0 4	3 7	3 2	7 7	16 5	ca 6 0	2 8

Includes all cases

Includes all cases with atrio-ventricular canal

In the material mentioned Anomalous pulmonary venous drainage to SVC or RA probably included both partial and total

One combined with atrial septal defect

Including those with pulmonary hypertension.

Fallot's tetralogy not mentioned in the statistics but VSD and pulmonary stenosis (14 6 %) probably mostly Fallot

The pulmonary obstruction syndrome — in the text more than 10 %. Not specifically mentioned in the statistics — cf

Combined with transposition of great vessels patent ductus arteriosus, atrial septal defect ASD VSD pulmonary stenosis, Fallot's tetralogy and situs inversus.

Combined with aortic stenosis

TABLE II Age and sex distribution of predominating diagnostic groups (1 000 patients)

			Year groups				
	♂	♀	0–10	11–20	21–30	31–40	>40
Atrial septal defect	80	130	59	73	32	21	23
Ventricular septal defect	85	66	97	45	12	3	4
Patent ductus arteriosus	37	92	83	31	7	4	5
Pulmonary stenosis	48	51	46	34	10	3	6
Fallot s tetralogy	48	32	62	13	5	–	–
Coarctation of aorta	29	18	14	6	7	2	1
All cases	495	505	509	269	108	55	59

according to this classification and our material is compared with Abbott s autopsy material from 1936 and with some clinical materials (1—9) Only Wood s and our own material comprise patients of all ages Many of the other clinical series are mainly concerned with children, while Warburg and Hansen s material includes a very small number of children below the age of 5 years

Results and discussion

When we compare the clinical materials with Abbott's autopsy material we see that the clinical materials include few cases of dextrocardia, pericardial defects, aortic atresia, anomalies of coronary arteries, cor biloculare and cor triloculare as compared with Abbott s material It is also noted that only three cases of cor triatriatum has been diagnosed in the clinical cases On the other hand we see that isolated pulmonary stenosis was very rare in Abbott s cases while the incidence in the clinical cases is around 10 % It is now well known that the diagnosis of isolated pulmonary stenosis was seldom made before the introduction of the technique of cardiac catheterization We also note that the diagnosis of atrial septal defect was rarely made in Abbott's series compared with the clinical series The same applies to a lesser extent to ventricular septal defect The higher frequency in clinical materials of pulmonary stenosis, atrial septal defect and ventricular septal defect might indicate a good prognosis in these anomalies It is surprising to find that the diagnosis of patent ductus arteriosus was made with almost the same frequency in Abbott's as in most of the clinical materials One would think that the prognosis is equally good in patent ductus arteriosus as in the other anomalies mentioned

When we compare the clinical materials according to the year they are published, we find that patent ductus arteriosus and coarctation of the aorta are on the decline while atrial and ventricular septal defects are increasing in frequency This applies especially to materials mostly comprising children In our series of cases atrial septal defect is the most common anomaly, followed by

septal defect and patent teriosus These three main left-to-right shunt together % of all cases of congenital ase seen by us

II shows the sex distribution e main diagnostic groups As from other materials females ate with regard to atrial septal d patent ductus arteriosus re are more male patients seen tricular septal defect Fallot s and coarcation of the aorta the cases of congenital heart equally divided among the sexes men 495 cases women 505 cases

Table II also shows the age distribution in this material About half of the patients are below 11 years of age while about 1/4 of them are more than 21 years of age and 59 patients are more than 41 years old The oldest patient was a 68-year-old man with atrial septal defect

The inclusion of idiopathic pulmonary hypertension among cases with congenital heart disease is somewhat doubtful Most of the patients seen by us are adults mostly women in the age group 20 40 years The etiology of this condition is not known Some consider these cases to be due to an inborn tendency of the pulmonary arteries to react with pulmonary hypertension to slight stimuli We feel that most of these cases are due to recurrent pulmonary embolism

It is of interest to note that the distribution of the cases of "Eisenmenger's syndrome" is almost the same among patent ductus arteriosus ventricular septal defect and atrial septal defect in our cases as in those of Wood When we calculate the percentage of patients developing severe pulmonary hypertension in the various groups of left to right shunt we find that the incidence is as follows Patent ductus arteriosus 12 % ventricular septal defect 26 % atrial septal defect 6 % This is almost the same percentage as was found by Wood and it shows that the site of the shunt is very important in the development of pulmonary hypertension in these cases

Summary

One thousand cases of congenital heart disease are reviewed with regard to anatomical diagnosis On comparison with other clinical materials an increasing frequency of septal defects was found depicting the trend in cardiac surgery of later years Severe pulmonary hypertension was found in 12 per cent in cases of patent ductus arteriosus in 26 per cent of ventricular septal defect and only in 6 per cent of atrial septal defect

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Haemorrhagic Diathesis Due to Criminal Poisoning with Warfarin

By

Eero Ikkala, Gunnar Myllylä, H R Nevanlinna, Risto Pelkonen and Kalevi Pyörälä

This case concerns a problem patient who for 2 1/2 years had an intermittent deficiency of prothrombin and factors VII, IX and X which caused bleeding symptoms The patient had to spend a total of 109 days in hospital because of his disease had one operation 15 roentgenological examinations and about 400 laboratory tests The final solution of the problem was surprising and dreadful — the recurrent bleeding symptoms were caused by rat poison containing warfarin which the patient s wife had surreptitiously fed her husband

Case report

The patient was a carpenter born in 1893 He had been healthy previously and there was no familial history of bleeding tendency

In December 1960 he was admitted to the local hospital because of haematuria and abdominal and dorsal pain He was found to have anaemia Hb 8 8 g 100 ml) an elevated ESR of 60 mm hour Intravenous pyelography gave a finding suggestive of an expansive process in the upper pole of the left kidney Nephrectomy was performed for suspected hypernephroma The kidney was hypertrophic but no tumour tissue was demonstrated histologically The patient was given 5 pints of blood in connection with surgery No haemostatic studies were made

The patient was readmitted to the same hospital a month later for bruises and intestinal haemorrhage His haemoglobin value was 5 5 g/100 ml whole blood clotting time 26 min He was treated with parenteral vitamin K and made a rapid recovery

A few months later the patient was again admitted to hospital for bruises epistaxis and gingival haemorrhage In addition to a slightly prolonged clotting time his prothrombin time was five times the normal Examinations for liver damage and malabsorption gave normal findings The patient s symptoms again disappeared quickly after administration of vitamin K

There followed a year without symptoms and then in Nov 1962 the patient was once again admitted for bleeding symptoms The prothrombin time was lengthened on this occasion too and again it was corrected by vitamin K

The haemorrhagic symptoms recurred after a couple of months and the patient was referred to the First Medical Department University of Helsinki He had melaena and large bruises on admission In addition to slight anaemia

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the whole blood clotting time was somewhat prolonged and the Thrombotest value was 5 % The bleeding time was normal, likewise the platelet count The patient was given 1 pint of blood and 20 mg of vitamin K_1 (Konakion®) intravenously A more thorough coagulation factor analysis was performed 2 days later The prothrombin and factor VII, IX and X concentrations were 60—70 % of normal, whereas the factor V and VIII assays, fibrinogen, and euglobulin clot lysis time were normal The prothrombin and the factor VII, IX and X levels were completely normal a few days later It was now clear that the recurrent bleeding symptoms were due to depression of clotting factors dependent on vitamin K, and that the defect was readily corrected with parenteral vitamin K_1 In searching for a clue to explain this abnormality we concentrated on the following points

1) Deficiency of vitamin K It seemed unlikely, because the patient was well nourished and there was no evidence of biliary obstruction or intestinal malabsorption The vitamin A and E and d xylose loading tests gave normal results

2) Impairment of liver function This was readily excluded, because serum bilirubin, alkaline phosphatase glutamic-oxalacetic transaminase, the electrophoretic pattern of serum proteins, and bromsulphalein retention were normal

3) Drugs used by the patient He had used only two drugs in the last few months Somadril® (carisoprodol 350 mg) and Deltacyl® (prednisolone 0 5 mg and acetylsalicylic acid 300 mg) In provocative tests these drugs were found to be without definite effect on the clotting factors

The patient was discharged with strict instructions to return immediately the haemorrhagic symptoms reappeared

On May 10, the patient was admitted to the Second Medical Department for epistaxis and bruises The prothrombin and factor VII IX and X levels were 1—4 % of normal He received 10 mg of vitamin K_1 (Konakion®) intravenously A complete normalization of the coagulation status occurred in 9 days Investigations that had already been performed earlier were repeated and supplemented by e g duodenal intubation for pancreatic juice examination, and duodenal biopsy both of which gave normal findings The patient was discharged symptom free, and plans were made to try oral vitamin K_1 on the next occasion In order to follow the situation blood samples were taken at intervals of a few weeks In the specimen taken on June 17 the prothrombin and factor VII, IX and X levels were 5—10 % However, the patient did not enter hospital again until June 24, having received no medication in the interval The concentration of the coagulation factors mentioned had nevertheless risen to the 30—50 % level and was completely normal in a few days

A point that had been taken into consideration throughout was the possibility of drugs acting in the manner of coumarin anticoagulants as the cause of the changes of the clotting mechanism However, the patient did not admit having taken any drugs during the last 4 months It was light heartedly suggested to the patient that perhaps somebody was trying to do away with him by giving him rat poison — though there did not seem to be any point in poisoning an old man But from this lead emerged the fact that the patient and his wife had been on extremely bad terms for years

A chemical method for the determination of warfarin was introduced at our laboratory for other purposes at the end of June This offered us a chance of testing the plasma samples of the patient for the presence of drugs of the coumarin group Plasma samples taken in May 10 and June 17, which had been stored at — 20°, were extracted according to O Reilly et al (9) Extracts of the patient s plasma and normal plasma to which pure warfarin had been added were found to give similar absorption spectra with an absorption maximum at 308 millimicrons Concentration of warfarin in the plasma sample taken on May 10 was found to be 6 mg/l and that of the plasma sample taken on June 17 2 5 mg/l

The result was explained to the patient and the matter was referred, with his consent, to the Central Criminal Police for investigation. Suspicion immediately fell on the patient s wife, aged 64 who admitted her guilt after repeated and protracted questioning She had been in the habit of pouring into the juice concentrate used by her husband doses of the 0 5 % warfarin liquid sold as rat poison As a precaution, she even bought the solution not in her home district but in a nearby town The wife has been arrested but the legal proceedings have not been concluded

Discussion

Misuse of anticoagulant drugs is a rare cause of haemorrhagic diathesis We have found in the literature 10 case reports, in which the patients — all associated with the medical profession — took the anti coagulant surreptitiously in order to pro duce bleeding symptoms (1, 2, 4, 8, 10, 11, 12) Accidental poisoning caused by anti-coagulant drug taken by mistake (4) and by rodenticide containing warfarin (5) have also been reported

Coumarin anticoagulants are incon-venient drugs for suicidal or homicidal purposes, because a single dose even when massive does not readily cause bleeding symptoms Holmes and Love (3) how-ever have reported a case in which the patient attempting suicide developed bleeding symptoms after ingesting 567 mg of warfarin during six days Criminal use of warfarin for poisoning another person has earlier been reported by Nilsson (6)

Arriving at the diagnosis took a long time in all the cases of misuse of anticoag ulants cited above, as it did in our own case The main reason is probably that the history given by the patient does not point to the right source of the trouble, even when he takes the anticoagulant on his own initiative not to mention the cases of attempted poisoning However the simultaneous depression of prothrombin factor VII factor IX and factor X to low levels in a person in whom no cause for deficiency of vitamin K and no signs of liver failure can be shown and who sub-sequently responds well to vitamin K should arouse suspicion of the ingestion of coumarin drugs Some other drugs can cause a slight depression of these coag ulation factors but only one of them acetylsalicylic acid, has been reported to cause bleeding symptoms (7) As far as we know, a proven congenital or acquired idiopathic deficiency of these factors has not been described The diagnosis of haemorrhagic diathesis due to misuse of anticoagulants is facilitated greatly by modern chemical methods for the assay of coumarin anticoagulants in plasma and other biological fluids

Summary

A patient had $2\,^1/_2$ years of intermittent prothrombin and factor VII, IX and X deficiency and consequent severe bleed ing symptoms The mysterious disease picture was found to be caused by rat poison containing warfarin which the pa tient s wife used to try to poison him

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Heart Volume and its Relation to Anthropometric Data in Old Men Compared with Young Men[1]

By

T STRANDELL

In order to estimate whether or not a certain heart volume is normal or abnormal for an individual roentgenologically determined heart volumes have been correlated to different indicies of body size such as weight height and calculated body surface area (4 18, 24, 26) Better correlations however have been obtained by relating the heart volume to the volume of the total cardiovascular system in normal individuals e g the total blood volume or the total haemoglobin (14 18) When tested together as independent variables in multiple regression analysis both total haemoglobin and weight were found to be significant for the heart volume in a mixed material of men and women including athletes (17) The significance was however highest for total haemoglobin

A high correlation has also been observed between heart volume and different cardiovascular functions such as the working intensity at heart rate 170 beats min (14 18) the heart rate or oxygen pulse during submaximal exercise at a fixed work load (20 21 26) and the oxygen uptake or oxygen pulse at maximal working intensity (3 20 21 26)

Concerning the correlation between heart volume and age the reports are contradictory, some showing a slight increase in volume with age in healthy individuals (6 24), others observing no increase with age (17, 20 21)

The purpose of the present investigation was to study the relationships between heart volume and several parameters such as age electrocardiographic findings, body size dimension of the cardiovascular system (blood volume or total haemoglobin) and some measurements of the cardiovascular function such as working intensity at heart rate 130 (oxygen pulse during exercise) in a material of healthy men of different ages

Material

In a previous study (29) the selection and examination of a material of 126 healthy males aged 30–83 years was discussed Another five subjects were rejected because of bundle branch block in the electrocardiogram /2/ signs of old myocardial injury in the ECG /1/, angina pectoris during the exercise test (never before) /1/ or because they had never bicycled before /1/ The present material consisted of 74 of these 121 men Below the age of 60 the

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Heart Volume and its Relation to Anthropometric Data in Old Men Compared with Young Men[1]

By

T Strandell

In or ler to est mate wl ether or not a certa n l eart volume is normal or abnormal for an ndividual roentgenolog cally determ ned heart volumes have been correlated to d fferent ind c es of body s ze s cl as weigl t l e gl t and calculated bod s rface area (4 18 24 26) Better correlat ons however have been obtained by relat ng tl e l eart volume to tl e vol ume of tl e total card ovascular s stem in normal i d v duals e g tl e total blood vol me or tl e total l eamoglol n 14 18) Wl en tested togetl er as independent var ial les m lt ple regress on analys s botl total l aemoglol n a l v e gl t v ere fo n l to be s gn l ant for tl e l eart vol me a m xed mater al of men and wom en incl l n atl letes 17 Tl e s gn f cance v a l ever l gl e t for to al l ae nogl l

A l gl rrelat on l as al o been observed bet een l ea t v lume a l d fferent car l o a c lar f n t ns s cl as tl e ork ng in en ty at l eart rate l 0 beats m n 14 18 tl e l eart rate or oxygen p l e l ng s l max mal exerc e at a f xed v k loa l 20 21 26 a l tl e oxygen ptake r ox gen p l e at maximal working i te ty 3 20 21 26

Concerning the correlat on between heart volume and age the reports are con trad ctory some sl o v ing a slight increase in volume with age in healthy ind viduals (6 24) others observing no increase with age (17 20 21)

The purpose of tl e present inve tiga on v as to study the relationsh ps between heart volume and several parameters s ich as age electrocard ograph c find ngs body size d mens on of the card ovascular system (l lood volume or total haemoglob n) and some measurements of the card ovascular function s ch as v orking intensity *at heart rate 130* (oxygen pulse during exerc e) in a material of healthy men of d fferent ages

Material

In a p ev ous s u ly (29 tl e select on and exam na on of a ma er al of 126 heal hy males aged *30—83* years was d scussed Ano her f e s bjec s ere rejected because of bundle bran h block n the electroca d ogram /2/ s gns of old m ocard al injury n the ECG /1/ ang na pector s during tl e exercise test (never before l o beca use hey had ne er b cycled before l The present material cons s ed of 74 of these 121 men Below the age of 60 the

S m ed r p a n Jan ary 3 1964

[1] A prel m nary report was g en a h ann al meet ng of he Swed sh Med cal Soc y n Nov mber 1963

wise increased work loads (every sixth minute) on a bicycle ergometer in sitting position starting at 300 kpm/min. Heart rate was determined from electrocardiographic recordings. The working intensity at heart rate 130 (W_{130} kpm/min.) was determined by intrapolation, in some cases by a short extrapolation. W_{170} was determined in a similar way. The 2–6 minute heart rate increase at heart rate 130 (St st_{130}) was determined by intra- or extrapolation from the values recorded at different work loads. The mean value was 7.1 ± 4.2 beats/min. A more complete description of the test was given in a previous report (30).

Lactic acid

The lactate concentration of arterialized finger blood was determined in 54 cases by the method of Barker and Summerson as modified by Ström (32). The method and its errors were discussed in greater detail in an earlier report (30). As the logarithm of the lactate concentration during exercise was approximately linearly related to heart rate, the log lactate concentration at heart rate 130 (Log $lact_{130}$) was estimated by intra- or extrapolation from the values recorded at different work loads. The mean value for Log $lact_{130}$ was 0.50 ± 0.16 (± SD) log mE/l or 3.15 mE/l

$$\left(SD = \begin{matrix} +1.40 \\ -0.95 \end{matrix}\right)$$

Electrocardiography

A complete description of the leads and techniques used and an assessment of the findings were given in a previous report (29). Only some details will be added here. At rest and after exercise leads I, II, III, CR_{1-7} were recorded, during exercise only leads CH_{1-7} (indifferent electrode on the forehead). The electrocardiographic findings were divided into five classes, class 1 being normal and 5 being regarded as abnormal. The same standars were used in all age groups. A horizontal or sagging ST segment depression ≥ 0.5 mm at rest, during or after exercise was regarded as abnormal as were frequent ventricular or supraventricular ectopic beats, two or more in a series, or ectopic beats from more than one focus. No abnormal T waves (negative) were recorded. The total assessment of the ECG was based on the most marked abnormality recorded. ECG_{tot} stands for the total assessment at rest and during the exercise test, ECG_{ST} for the corresponding assessment of ST. ECG_{EB}, ECG_{VEB} and ECG_{SVEB} correspondingly denote the assessment of ectopic beats, ventricular ectopic beats and supraventricular ectopic beats.

Total haemoglobin, blood volume and haemoglobin concentration

The methods used for these determinations will be described in a following paper (31). Total haemoglobin was determined with the alveolar CO method.

Statistical calculations

These were made according to Snedecor (28). The following probability (P) levels of significance were used: $P < 0.001$*** highly significant, $P < 0.01$** significant and $P <$ < 0.05* probably significant.

Multiple regression analysis was performed by the method of least squares in order to study the relationships between the functional parameters heart volume, total haemoglobin, blood volume, W_{130} and some other anthropometric data. The regressions were expressed according to the equation $y = a + b_1 x_1 + + b_2 x_2 + \ldots + b_n x_n$, where y is the dependent variable. Under certain circumstances the equation $y = a\, x_1^{b1}\, x_2^{b2} \ldots x_n^{bn}$ is a better theoretical approach, e.g. when the regression between data with different dimensions are studied (e.g. length, area, volume). These equations should also be more physiologically meaningful when the regression lines or hyperplanes theoretically must pass through origo (e.g. at zero height the heart volume must be zero) and when values both close to and far from origo are to be studied. In the present study both types of regression equations were computed. As the residual standard deviations were similar with both methods, the linear regression equations which are simpler to use are given in the tables.

It must be mentioned that age was not a normally distributed variable in the present study but was used for selection of the material. Furthermore, both the assessments of the electrocardiographic findings and the anamnestic degree of physical activity were discontinuous variables and showed a skew distribution in the different age groups. The use of these parameters in correlation studies should then not be strictly correct, but quite correct in regression studies as independent variables.

subjects were randomly selected from these 121 men. Above 60 years of age all subjects were invited but three of them did not participate owing to lack of time and interest. Three further subjects were excluded on account of the multiple regression analysis. In one of these the determination of heart volume was lacking, and in the other two the determination of total haemoglobin and blood volume.

The degree of physical activity at examination and earlier in life was anamnestically estimated in 70 subjects and crudely recorded in three classes, class one denoting no regular physical training, class two a moderate degree of training and class three a high degree of training such as hard bicycling every day, cross country running, or hard work, e.g. in the building trade.

At all ages the fraction of subjects with abnormal or suspected abnormal ECG-changes at rest or during the exercise test was similar to the findings in the total material (29). The mean working intensity at heart rate 130 (W_{130}) was not changed by the further selection except in the 40–49 year group where the subjects in the present study showed a higher value (+157 kpm/min, $P < 0.05$) than those who were not invited. This higher W_{130} in the presently studied 40–49 years old subjects may be associated both with the greater weight of the subjects (+6.6 kg) and with their higher degree of physical activity (+0.5 according to the scale given above).

Methods

Heart volume

The heart volume was determined in the prone position (22). The advantages of determining the heart volume in prone instead of standing position were discussed by Larsson et al. (22). Much better reproducibility of the heart volume determination in prone compared to standing position was also found by Musshoff et al. (25). This may especially be attributed to the varying influence of orthostatic blood volume displacements on the heart volume in standing position.

In order to better visualize the lower heart contour, the frontal pictures were taken with the tube angled 30° towards the feet (16, 18). However, the frontal and sagittal pictures were not exposed simultaneously, and bore no relation to ECG and heart cycle. They were taken while the subject held his breath after deep inspiration. Care was taken to avoid a Valsalva or Muller manoeuvre. In 53 cases pictures were also taken during superficial respiration. The difference between the heart volume during held inspiration and superficial respiration was not significant, 4 ± 38 ml (mean ± SD). This is in agreement with earlier reports (16). The coefficient of variation for the heart volume determination was 3.2 % computed from the differences mentioned above. This figure also corresponds to earlier findings (16, 22).

When the tube was angled 30° towards the feet the rays in the frontal projection were no longer perpendicular to the film. The projection error thus obtained was studied by Kjellberg et al. (16) who found that it varied with the shape of the heart in the same direction as the form factor (F) given by Larsson et al. (22): $V = F \cdot l \cdot b \cdot d$, where V is the volume in ml, l (the length) is the greatest longitudinal diameter of the elliptical figure in the posteroanterior projection, b (the width) is the greatest diameter in the lateral view. All heart diameters are given in cm corrected for the magnification. F is a variable function of $\frac{d}{l \cdot b}$ determined empirically. F was highest for flat hearts with low $\frac{d}{l \cdot b}$. Kjellberg et al. (16) considered the projection error to be without practical significance except possibly in cases of very flat heart.

However, with angulation of the tube the volume of a spherical heart will be overestimated by 13 per cent (12). For a more normally shaped heart the projection error will depend on the shape of the heart and on its position in the thoracic cage and both positive and negative errors may appear. The magnitude of the mean projection error of fairly normal hearts has not yet been investigated completely, but is probably of the order of 5 per cent (12). In the present study no individual correction for the projection error was found possible and no mean correction was used.

Exercise test

Before the exercise test was performed the heart rate at rest in supine (66.3 ± 9.9 beats/min, mean ± SD, $n = 74$) and standing position (80.9 ± 14.1) was counted. The mean heart rate increase in standing position was 14.6 ± 8.9. The exercise test consisted of step-

Table II Some correlation coefficients between weight, total haemoglobin (THb) heart volume (HV) and rate of work at heart rate 130 beats/min (W_{130}) in men of different ages

Age group (yrs)	No of individ	Weight–THb	Weight–HV	Weight–W_{130}	THb–HV	THb–W_{130}	HV–W_{130}
30–39	22	0 80***	0 47*	0.27	0 56**	0.20	0 40
40–49	11	0 89***	0.83***	0 80**	0 90***	0 76**	0 87***
50–59	10	0 89***	0.85**	0 63	0 85**	0 73*	0 49
60–69	17	0 67**	0 71**	0 30	0 60*	0 30	0.21
70–75	10	0.82**	0 58	0 47	0 75*	0 69*	0 69*
80–83	4	0 91	0 90	0 72	0 91	0 91	0 66
[1]30–83	74	0 81***	0 64***	0 31**	0 74***	0 50***	0 40***

[1] Mean values calculated after conversion to z

As estimates of the oxygen pulse during exercise both W_{170} W_{130} and heart rate at 600 kpm/min were tested in the regression studies It was observed that the correlation coefficients with heart volume total heamoglobin and blood volume were just the same for W_{170} W_{130} and heart rate at 600 kpm/min With heart volume they were 0 47 0 50 and —0 50 respectively (n = 71) with total haemoglobin they were 0 47 0 50 and —0 50 and with blood volume 0 48, 0 49 and —0 50 As W_{170} could not be determined in 3 subjects owing to low maximal heart rates W_{130} was used in the regression analysis, the correlation coefficient between these two variables being 0 92 (n 71)

The relationships between age and some parameters are given in table III The regression on age of ECG_{total} Log $lact_{130}$ St st_{130} and the anamnestic degree of physical activity earlier in life was highly significant and positive The regression on age of heart volume was positive and of probable significance as was the negative regression on age of heart rate increase in standing position

Table III Regression coefficients (b) between age (independent variable, x) and some anthropometric data (dependent variable y) and the significance of b in 74 healthy men aged 30—83 years St st_{130}= 2—6 min heart rate increase at heart rate 130 (beats/min) Physical activity = scale 1—3, (see material) Other symbols as in tables I and IV For log $lact_{130}$ n=54, for physical activity n=70

Dependent variable	b	b/εb
Weight	0 02	0 24
Height	−0 06	−1.26
Heart volume	2 63	2 35*
Total haemoglobin	−0 99	−1 15
Haemoglobin conc.	−0 008	−1.25
Blood volume	−0 004	−0 67
Heart rate supine	0 07	0 09
Heart rate standing	−0 13	−1.29
Heart rate st sup	−0 14	−2 21*
W_{130}	0 32	0.27
St st_{130}	0 11	3 70***
Log $lact_{130}$	0 005	4 14***
ECG_{total}	0 05	5 83***
Physical activity		
at examination	0 01	1.26
earlier in life	0 02	3.90***

Heart volume as dependent variable

When the heart volume was studied as the dependent variable in regression and multiple regression analysis the results in table IV were obtained

The lowest residual standard deviation was obtained with weight as the independent variable (fig 1) followed by total haemoglobin (fig 2), body surface area,

Table I Height, weight, body surface area (BSA), total haemoglobin (THb), haemoglobin concentration (Hb conc), blood volume (BV), heart volume (HV) and intensity of work at heart rate 130 beats/min (W_{130}) and at 170 beats/min (W_{170}) in 74 men aged 30—83 years Mean values ± SD

Age group (yrs)	No of individ	Age (yrs)	Height (cm)	Weight (kg)	BSA (m²)	THb (g)	Hb conc (g/100 ml)	BV (l)	HV (ml)	W_{130} (kpm/min)	W_{170} (kpm/min)
30—39	22	34 3 ± 2 5	176 3 ±7 2	71 7 ±7 6	1 89 ±0 13	796 ±118	13 56 ±0 83	5 87 ±0 77	768 ±102	600 ±149	950 ±1[illegible]3
40—49	11	44 4 ± 2 7	175 6 ±6 6	76 8 ±9 8	1 93 ±0 15	822 ±139	13 15 ±0 82	6 27 ±1 12	846 ±173	737 ±143	1103 ±181
50—59	10	54 7 ± 3 0	172 9 ±6 4	70 4 ±9 1	1 84 ±0 14	781 ±119	12 98 ±1 08	6 03 ±0 89	805 ±125	638 ±218	1001 ±[illegible]3
60—69	17	65 7 ± 2 9	174 4 ±6 5	73 8 ±10 5	1 89 ±0 14	766 ±101	13 38 ±0 86	5 73 ±0 67	867 ±155	634 ±149	1008 ±226
70—75	10	72 2 ± 1 6	173 3 ±4 0	73 4 ±9 6	1 87 ±0 12	760 ±117	13 31 ±1 22	5 70 ±0 59	834 ±179	637 ±146	[1]95[illegible] ±171
80—83	4	81 3 ± 1 3	175 5 ±8 5	72 5 ±15 3	1 88 ±0 21	774 ±165	12 80 ±0 67	6 02 ±1 06	981 ±335	655 ±158	[2]8[illegible]0 ± [illegible]
30—83	74	53 4 ±16 0	174 9 ±6 5	73 0 ±9 4	1 89 ±0 11	785 ±118	13 30 ±0 92	5 90 ±0 82	828 ±160	641 ±160	[3]99[illegible] ±20[illegible]

[1] The number of individuals = 9

[2] The number of individuals = 2

[3] The number of individuals = 71

Results

The mean values in the different decades of some of the measured parameters are given in table I

There were no differences of probable significance regarding total haemoglobin, haemoglobin concentration or blood volume between the different age groups The heart volume was larger in the 80—83 compared with the 30—39 year group (t-test, $P < 0\ 05$) W_{130} was higher in the 40—49 than in the 30—39 year group (t test, $P < 0\ 05$), which may be connected both with heavier weight and higher degree of physical training

Some correlation coefficients between weight, total haemoglobin heart volume and W_{130} are given in table II The highest correlations were obtained in the 40—49 year group, and some of the lowest in the 30—39 and the 60—69 year group Besides random variation this may in part be attributed to varying degree of physical training in the different decades The highest correlations between heart volume total haemoglobin and W_{130} might be expected in the groups with highest and most homogenous degree of physical training As the correlation coefficients in the different ages, however, were not drawn from different populations (tested after conversion to z, $P > 0\ 1$) the average r's were calculated In the subsequent study the material was treated as one population

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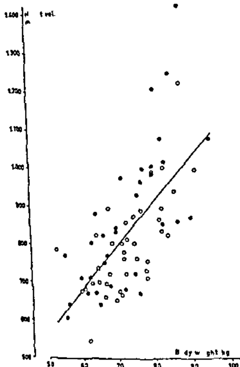


Fig 1 Heart volume in relation to body weight in 74 healthy men aged 30—83 years Open circles denote subjects aged 30—55 years filled circles denote subjects aged 56—83 years Regression line (section 1 table IV) ± 2 SD

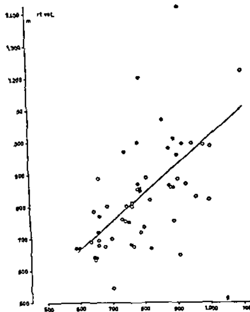


Fig 2 Heart volume in relation to total haemoglobin in 74 healthy men aged 30—83 years Symbols as in fig 1 Regression line (section 1 table IV) ± 2 SD

blood volume W_{130} height and ECG$_{total}$ (section 1) Body surface areas were calculated by Du Bois height weight formula Besides the correlations listed in table IV the heart volume was also significantly correlated to Log lact$_{130}$ r — — 0 42 n 54) heart rate in standing position (HR_{st}) (r —0 33 n 74) ECG$_{1s}$ (0 32) and probably significantly correlated to ECG$_{VE4}$ (0 29) heart rate increase in standing position (—0 27) a e (0 27) 2—6 minute heart rate increase at 600 kpm min (—0 26) and heart rate at rest supine (—0 23)

The regression of heart volume y) on total haemoglobin x) was computed both for the subjects aged 30—55 years y 204 + 0 734x SD — 90 ml, r = 0 71 n = 38) and those aged 56—83 years (y — 64 + 1 213x SD — 127 r = 0 74 n — 36) The slope of the regression line was steeper ($P < 0.05$) in the older half of the material compared to the younger half No differences of probable significance were found as regards the regression of heart volume on weight in the older and younger halves of the material

When the regression computations were performed with two significant independent variables section 2 table IV) the lowest residual standard deviations were obtained with weight as one of the variables and ECG$_{to}$, age HR_{st} blood volume and total haemoglobin as the

Table II Heart volume (y) in ml in relation to weight (kg), total haemoglobin (THb, g) body surface area (BSA, m²), blood volume (BV, l), W_{130} (kpm/min), height (cm), the total assessment of ECG at rest and during the exercise test (ECG_{total}, scale 1—5), age (years), heart rate in standing position (HR_{st}, beats/min), heart rate increase in standing position (HR_{st-sup}, beats/min and log arterial lactate concentration at heart rate 130 (log $lact_{130}$ log mE/l) in 74 healthy men aged 30—83 years The section number indicates the number of independent variables Mean value ± SD for heart volume = 828 ± 161 ml or ± 19.4 % of the mean In the last regression in section 4, n = 54

Section	Independent variable	Regression equation	Residual standard deviation ml	Residual standard deviation % of mean	b/εb	r	R
1	Weight	$y = -27 + 11.7x$	117	14.1	8.03***	0.690	
	THb	$y = 139 + 0.878x$	124	14.9	7.15***	0.644	
	BSA	$y = -571 + 742x$	124	15.0	7.08***	0.641	
	BV	$y = 89 + 125x$	125	15.1	7.00***	0.637	
	W_{130}	$y = 521 + 0.478x$	142	17.2	4.58***	0.475	
	Height	$y = -904 + 9.91x$	148	17.9	3.70***	0.399	
	ECG_{total}	$y = 708 + 42x$	150	18.1	3.43***	0.375	
2	Weight (x_1)	$y = -106 + 11.3x_1 + 37x_2$	105	12.7	8.71***		0.7[illegible]
	ECG_{total} (x_2)				4.28***		
	Weight (x_1)	$y = -152 + 11.6x_1 + 2.50x_2$	111	13.4	8.47***		0.733
	Age (x_2)				3.08**		
	Weight (x_1)	$y = 237 + 11.2x_1 - 2.79x_2$	111	13.4	8.07***		0.732
	HR_{st} (x_2)				-3.01**		
	Weight (x_1)	$y = -117 + 8.13x_1 + 59.6x_2$	112	13.6	4.18***		0.7[illegible]
	BV (x_2)				2.65**		
3	Weight (x_1)	$y = -198 + 7.70x_1 + 37x_2 - 60.4x_3$	99	12.0	4.48***		0.7[illegible]
	ECG_{total} (x_2)				4.59***		
	BV (x_3)				3.04**		
	Weight (x_1)	$y = -275 + 7.35x_1 - 2.85x_2 + 70.2x_3$	103	12.5	4.08***		0.7[illegible]
	Age (x_2)				3.72***		
	BV (x_3)				3.35**		
	Weight (x_1)	$y = -223 - 6.33x_1 - 3.12x_2 - 0.538x_3$	104	12.6	2.98**		0.7[illegible]
	Age (x_2)				3.94***		
	THb (x_3)				3.12**		
4	Weight (x_1)	$y = -154 + 7.56x_1 + 32x_2 - 61.1x_3 - 3.00x_4$	96	11.6	4.53***		0.812
	ECG_{total} (x_2)				4.03***		
	BV (x_3)				3.17**		
	HR_{st-sup} (x_4)				-2.34*		
	Weight (x_1)	$y = -349 - 7.05x_1 - 29x_2 - 75.8x_3 - 284x_4$	103	12.5	3 3**		0.811
	ECG_{total} (x_2)				2.64**		
	BV (x_3)				2.58*		
	Log $lact_{130}$ (x_4)				2.95**		

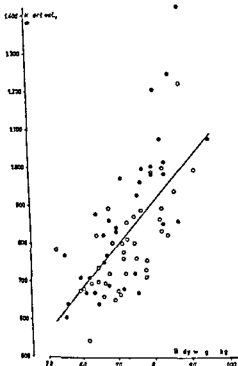


Fig 1 Heart volume in relation to body weight in 74 healthy men aged 30 83 years Open circles subjects aged 30 55 years filled circles denote subjects aged 56 83 years Regression line (section 1 table IV) ± 2 SD

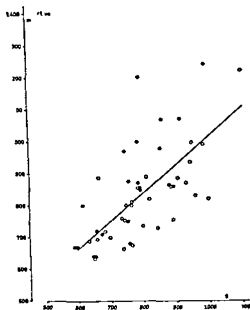


Fig 2 Heart volume in relation to total haemoglobin in 74 healthy men aged 30 83 years Symbols as in fig 1 Regression line (section 1 table IV) ± 2 SD

blood volume W_{30} height and ECG_{total} (section 1) Body surface areas were calculated by Du Bois height weight formula. Besides the correlations listed in table IV the heart volume was also significantly correlated to $Log\ lact_{30}$ r 0 42 n 51) heart rate in standing position (HR) r −0 33 n 74 ECG (0 32) and probably significantly correlated to ECG_{rs} 0 29 heart rate increase on standing position 0 27 and 0 2 6 minute heart rate increase at 600 kpm min 0 26) and heart rate at rest supine −0 23

The regression of heart volume on total haemoglobin was computed both for the subjects aged 30— years 204 + 0 734x SD − 90 ml r 0 71 n − 38) and those aged 56—83 years (y 64 + 1 213x SD − 127 r − 0 74 n 36) The slope of the regression line was steeper ($P < 0.05$) in the older half of the material compared to the younger half No differences of probable significance were found as regards the regression of heart volume on weight in the older and younger halves of the material

When the regression computations were performed with the significant independent variables section 2 table IV) the lowest residual standard deviations were obtained with weight as one of the variables and ECG_{tot} age HR_{st} blood volume and total haemoglobin as the

Table IV Heart volume (y) in ml in relation to weight (kg), total haemoglobin (THb, g), body surface area (BSA, m²), blood volume (BV, l), W_{130} (kpm/min), height (cm), the total assessment of ECG at rest and during the exercise test (ECG_{total}, scale 1—5), age (years), heart rate in standing position (HR_{st}, beats/min), heart rate increase in standing position ($HR_{st\text{-}sup}$, beats/min and log arterial lactate concentration at heart rate 130 (log $lact_{130}$, log mE/l) in 74 healthy men aged 30—83 years The section number indicates the number of indifferent variables Mean value ± SD for heart volume = 828 ± 160 ml or ± 19.4 % of the mean In the last regression in section 4, n = 54

Section	Independent variable		Regression equation	Residual standard deviation ml	Residual standard deviation % of mean	b/εb	r	R
1	Weight		$y = -27 + 11.7x$	117	14.1	8.08***	0.690	
	THb		$y = 139 + 0.878x$	124	14.9	7.15***	0.644	
	BSA		$y = -571 + 742x$	124	15.0	7.08***	0.641	
	BV		$y = 89 + 125x$	125	15.1	7.00***	0.637	
	W_{130}		$y = 521 + 0.478x$	142	17.2	4.58***	0.475	
	Height		$y = -904 + 9.91x$	148	17.9	3.70***	0.399	
	ECG_{total}		$y = 708 + 42x$	150	18.1	3.43***	0.375	
2	Weight	(x_1)	$y = -106 + 11.3x_1 + 37x_2$	105	12.7	8.71***		0.765
	ECG_{total}	(x_2)				4.28***		
	Weight	(x_1)	$y = -152 + 11.6x_1 + 2.50x_2$	111	13.4	8.47***		0.733
	Age	(x_2)				3.08**		
	Weight	(x_1)	$y = 237 + 11.2x_1 - 2.79x_2$	111	13.4	8.07***		0.73[illegible]
	HR_{st}	(x_2)				-3.01**		
	Weight	(x_1)	$y = -117 + 8.13x_1 + 59.6x_2$	112	13.6	4.18***		0.723
	BV	(x_2)				2.65**		
3	Weight	(x_1)	$y = -198 + 7.70x_1 + 37x_2 + 60.4x_3$	99	12.0	4.48***		0.796
	ECG_{total}	(x_2)				4.59***		
	BV	(x_3)				3.04**		
	Weight	(x_1)	$y = -275 + 7.35x_1 + 2.85x_2 + 70.2x_3$	103	12.5	4.08***		0.775
	Age	(x_2)				3.72***		
	BV	(x_3)				3.35**		
	Weight	(x_1)	$y = -223 + 6.33x_1 + 3.12x_2 + 0.538x_3$	104	12.6	2.98**		0.771
	Age	(x_2)				3.94***		
	THb	(x_3)				3.12**		
4	Weight	(x_1)	$y = -134 + 7.56x_1 + 32x_2 + 61.1x_3 - 3.06x_4$	96	11.6	4.53***		0.812
	ECG_{total}	(x_2)				4.03***		
	BV	(x_3)				3.17**		
	$HR_{st\ sup}$	(x_4)				-2.34*		
	Weight	(x_1)	$y = -349 + 7.05x_1 + 29x_2 + 73.8x_3 + 284x_4$	103	12.5	3.[illegible]3**		0.811
	ECG_{total}	(x_2)				2.84**		
	BV	(x_3)				2.58*		
	Log $lact_{130}$	(x_4)				2.95**		

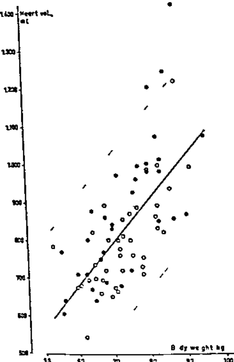


Fig 1 Heart volume in relation to body weight in 74 healthy men aged 30—83 years. Open circles denote subjects aged 30—55 years filled circles denote subjects aged 56—83 years. Regression line (section 1 table IV) ± 2 SD

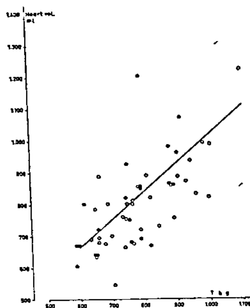


Fig 2 Heart volyme in relation to total haemoglobin in 74 healthy men aged 30—83 years Symbols as in fig 1 Regression line (section 1 table IV) ± 2 SD

blood volume W_{136} height and ECG_{total} (section 1) Body surface areas were calculated by Du Bois height weight formula Besides the correlations listed in table IV the heart volume was also significantly correlated to Log $lact_{136}$ (r = = 0 42 n = 54) heart rate in standing position (HR_s) (r = —0 33 n = 74) ECG_E (0 32) and probably significantly correlated to ECG_{VE_3} (0 29) heart rate increase in standing position (—0 27) age (0 27) 2—6 minute heart rate increase at 600 kpm/min (—0 26) and heart rate at rest supine (—0 23)

The regression of heart volume (y) on total haemoglobin (x) was computed both for the subjects aged 30—55 years (y = 204 + 0 734x, SD = 90 ml r = 0 71, n = 38) and those aged 56—83 years (y = 64 + 1 213x SD = 127, r = 0 74 n = 36) The slope of the regression line was steeper ($P < 0.05$) in the older half of the material compared to the younger half No differences of probable significance were found as regards the regression of heart volume on weight in the older and younger halves of the material

When the regression computations were performed with two significant independent variables (section 2 table IV) the lowest residual standard deviations were obtained with weight as one of the variables and $ECG_{tot\,I}$ age HR_s blood volume and total haemoglobin as the

Table IV Heart volume (y) in ml in relation to weight (kg), total haemoglobin (THb, g), body surface area (BSA, m^2), blood volume (BV, l), W_{130} (kpm/min), height (cm), the total assessment of ECG at rest and during the exercise test (ECG_{total}, scale 1—5), age (years), heart rate in standing position (HR_{st}, beats/min), heart rate increase in standing position (HR_{st-sup}, beats/min and log arterial lactate concentration at heart rate 130 (log $lact_{130}$, log mE/l) in 74 healthy men aged 30—83 years The section number indicates the number of indifferent variables Mean value ± SD for heart volume = 828 ± 160 ml or ± 19.4 % of the mean In the last regression in section 4, n = 54

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	Weight (x_1) Age (x_2)	$y = -152 + 11.6x_1 + 2.50x_2$	111	13.4	8.47*** 3.08**		0.733
	Weight (x_1) HR_{st} (x_2)	$y = 237 + 11.2x_1 - 2.79x_2$	111	13.4	8.07*** -3.01**		0.732
	Weight (x_1) BV (x_2)	$y = -117 + 8.13x_1 + 59.6x_2$	112	13.6	4.18*** 2.65**		0.725
3	Weight (x_1) ECG_{total} (x_2) BV (x_3)	$y = -198 + 7.70x_1 + 37x_2 + 60.4x_3$	99	12.0	4.48*** 4.59*** 3.04**		0.796
	Weight (x_1) Age (x_2) BV (x_3)	$y = -275 + 7.35x_1 + 2.85x_2 + 70.2x_3$	103	12.5	4.08*** 3.72*** 3.35**		0.775
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	Weight (x_1) ECG_{total} (x_2) BV (x_3) Log $lact_{130}$ (x_4)	$y = -349 + 7.05x_1 + 29x_2 + 73.8x_3 - 284x_4$	103	12.5	3.[illegible]3** 2.84** 2.58* 2.95**		0.811

significance was observed with supra ventricular ectopic beats

ST segment and ECG at rest The relationship between ECG_{ST} and heart volume was further studied in the subjects who were free from other types of changes in the ECG In these 42 subjects the difference between the observed heart volume and the value predicted from weight and blood volume (section 2, table IV) was computed The mean difference between observed and predicted heart volume was -78 ± 72 ml (mean $\pm$ SD $n = 16$) in the group with normal ECG_{ST} (class 1), -37 ± 78 ml (n = 13) in that with class 2, $+37 \pm 84$ ml (n = 8) in that with class 3, and $+89 \pm 128$ ml (n = 5) in that with suspected abnormal or abnormal ECG_{ST} (class 4 and 5) (fig 3) The difference between class 1 and 2 was not significant ($P > 0.1$) but the difference between class 1 and 3 was significant (t test) as also between class 1 and 4 + 5 When the difference between observed and predicted heart volume was studied as dependent variable in these 42 subjects, ECG_{ST} was highly significant (b = 50 ± 12.4) as independent variable when tested together with age which was not significant ($P > 0.3$)

In the total material the difference between the observed heart volume and the value predicted from weight and blood volume was studied as dependent variable in the same way Three assessments of the resting ECG were tested as independent variables together with age The assessment of the ST segment was probably significant ($b/s_b = 2.38^*$) with age ($b/s_b = 3.1^{**}$) the combined assessment of ST segment and ectopic beats was significant (2.66^{**}) with age (2.27^* and the total assessment of the resting ECG was probably significant (2.10^*) with age (2.18^*)

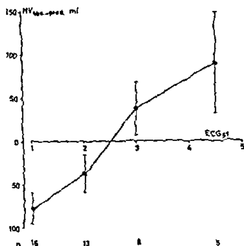


Fig 3 Observed heart volume less the value predicted from weight and blood volume ($HV_{obs-pred}$) in relation to the assessment of the ST segment of the ECG at rest and during the exercise test (ECG_{ST} scale 1–5) in 42 men aged 31–83 years free from other types of changes in the ECG

Shape of the heart and ECG As the heart volumes in the present study included a projection error which mainly affected the short axes of the elliptical area in the frontal plane (the width see Methods), the different heart diameters were tested as dependent variables It was found that ECG_{total} as independent variable was most significant for the length of the heart ($b/s_b = 3.12^{**}$) and the depth (2.40^*) less so for the width (2.0^*) When ECG_{total} and weight were tested together as independent variables, ECG_{total} was significant for length (3.42^{**}) and depth (2.52^{**}) but not significant for width (1.98) Thus the correlation between heart volume and ECG_{total} was not due to the projection error of the heart volume determination It would probably have been still better if the projection error had been avoided According to the regression coefficients when tested together with weight the following increases

other in that order The lack of correlation between ECG_{total} and weight ($r = 0.07$) thus caused ECG_{total} to be a more suitable independent variable together with weight than total haemoglobin and blood volume, which were significantly correlated to weight (table II)

When W_{130} was tested together with total haemoglobin or blood volume the *residual standard deviation* (± *14 6 %*) was greater than with weight alone W_{130} *lost its significance when tested together* with weight ($P > 0.05$), as also did height ($P > 0.8$) The anamnestic degree of physical activity at examination was not of probable significance for the heart volume ($r = 0.23$, $n = 70$) but the earlier physical activity was of probable significance ($r = 0.26^*$) However, neither of these variables was of probable significance ($P > 0.1$ and $P > 0.3$ respectively) when tested together with age as independent variable

Age lost its significance when tested together with ECG_{total} ($P > 0.6$) and the correlation between age and heart volume was thus attributed to the increase with age of electrocardiographic deviations from the normal According to the regression of heart volume on weight and ECG_{total} (section 2, table IV) the mean heart volume in the subjects with normal ECG_{total} was *760 ml* at a mean weight of 73 kg The mean increase of the heart volume in the cases with abnormal ECG_{total} was accordingly 150 ml or 19 per cent

The best three independent variables tested together were weight, ECG_{total} and blood volume or total haemoglobin (section 3, table IV) The more general equations with age instead of ECG_{total} are also given

The only variables tested that were of probable significance together with *weight*, ECG_{total} and blood volume, were heart rate increase in standing position (HR_{st-sup}) and *log arterial lactate at heart rate 130* (Log $lact_{130}$) (section 4, table IV) *A heart volume above the mean* was thus observed in cases with *low* HR_{st-sup} *or high Log* $lact_{130}$ *When* all five independent variables in section 4 *were tested together,* HR_{st-sup} *lost its significance* ($P > 0.1$) The correlation between heart volume and Log $lact_{130}$ cannot be explained by the present data *With the best four variables the residual standard* deviation decreased to ± *11 6* per cent of the mean heart volume compared to the original standard deviation of ± *19 4* per cent

Heart volume and electrocardiographic findings

Ectopic beats The correlation observed between heart volume and ECG_{total} was further studied As single independent variable the assessment of ectopic beats during the exercise test (ECG_{EB}) was of significance and ECG_{VEB} of probable significance for the heart volume, whereas ECG_{SVEB}, ECG_{ST} and the assessment of conduction disturbances (including extreme left axis deviation consistent with peri infarction block) were not When ECG_{EB} was studied as independent variable together with age, ECG_{EB} was found to be of probable significance whereas age was not When ECG_{ST}, ECG_{VEB} or ECG_{SVEB} were tested together with age, none of the variables were of probable significance Together with weight, however, both ECG_{VEB} and age were of probable significance as independent variables In the present material there was thus a probably significant correlation between heart volume and ectopic beats which was not lost when age was included as independent variable Further study showed this to be due to the ventricular ectopic beats whereas no correlation of probable

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ST segment and ECG at rest The relationship between ECG_{ST} and heart volume was further studied in the subjects who were free from other types of changes in the ECG In these 42 subjects the difference between the observed heart volume and the value predicted from weight and blood volume (section 2, table IV) was computed The mean difference between observed and predicted heart volume was -78 ± 72 ml (mean $\pm$ SD n = 16) in the group with normal ECG_{ST} (class 1), -37 ± 78 ml (n = 13) in that with class 2 $+37 \pm 84$ ml (n = 8) in that with class 3 and $+89 \pm 128$ ml (n = 5) in that with suspected abnormal or abnormal ECG_{ST} (class 4 and 5) (fig 3) The difference between class 1 and 2 was not significant ($P > 0.1$), but the difference between class 1 and 3 was significant (t test) as also between class 1 and 4 + 5 When the difference between observed and predicted heart volume was studied as dependent variable in these 42 subjects, ECG_{ST} wa higly significant (b = 50 ± 12.4) as independent variable when tested together with age, which was not significant ($P > 0.3$)

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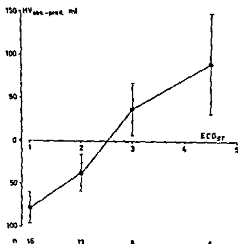


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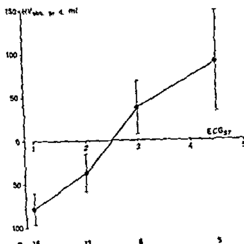


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in heart diameters were present in the subjects with abnormal ECG_{total} compared to those with normal electrocardiograms, length + 0 9 cm (6 %), width + 0 4 cm (4 %), depth + 0 7 cm (7 %)

The form factor of the heart (F) was not correlated to age, weight or ECG_{total}, but was correlated to height (r = 0 24*) According to the regression coefficient the form factor (F) (see Methods) was 1 per cent higher per 10 6 cm increase in height above the mean value This indicates that the tall subjects had flatter hearts (short depth) than shorter subjects If this form factor of Larsson et al (22) had not been used, the calculated heart volumes would have been slightly less correlated to height

Heart volume and arterial blood pressure In the total material (n = 74) a study was made of the correlation between the blood pressure and the difference between the observed heart volume and the value predicted from the weight and blood volume The correlation coefficient with the systolic blood pressure was + 0 24* but this significance was lost when the effect of age was eliminated, the partial correlation coefficient being — 0 05 The correlation coefficient with the diastolic blood pressure was not significant, neither the total (r = 0 12) nor the partial (r = 0 02)

Discussion

Physical activity

The degree of physical activity was in the present study only crudely estimated However, the significant increase in an amnestic activity earlier in life with rising age in the present material is consistent with the structural changes of society during the last 50 years in respect of living habits, heavy manual work and other factors

There was no correlation of probable significance between the heart volume and degree of physical activity, either at examination or earlier in life when the effect of age was corrected for This must be due either to the fact that the degree of physical activity varied so little in the present material that the effect on the heart volume did not appear as significant, or that the classification used was too crude or irrelevant The classification, however, has not been quite without importance in the present material, as the intensity of work at heart rate 130 (W_{130}) was significantly correlated to the physical activity at examination (31) In a previous study of former racing cyclists (15) it was shown that the large heart volumes of the athletes mainly remained unchanged despite their fairly normal physical activity at the time of the examination 18 years after the active period Their large heart volumes may thus have been due to their high degree of physical training earlier in life In these former athletes ST depressions in the exercise electrocardiogram and ectopic beats were, however, rather frequent, and similar findings in the present study were connected with large heart volumes

Heart volume as dependent variable

The present material includes normal men varying in body size, age and degree of physical activity Of the parameters studied the heart volume was in this material best correlated to body weight, followed by total haemoglobin and blood volume However, there was no difference of probable significance between the correlation between heart volume and these parameters In athletes, in whom physical training induces a marked circulatory

load, the values for heart volume, total haemoglobin and blood volume are all higher than in ordinary men (18), whereas weight is either unaffected or decreases with circulatory training Athletes thus have larger heart volumes in relation to weight than ordinarily trained men but seem to have the same relation between heart volume and total haemoglobin (18) When both body weight and total haemoglobin or blood volume were tested together as independent variables the significance of weight was highest in the present study In a previous study of athletes as well as ordinary men and women (17), the significance of total haemoglobin was on the contrary much higher than that of weight This difference between the findings in the two materials may well be explained by the absence of women and athletes in the present study and the fact that the variation in degree of physical training was consequently less The correlation with blood volume and total haemoglobin in the present material when considera tion was paid also to weight would thus be ascribed to varying degree of physical training or possibly to dispositional varia tions in the relationship between weight and the size of the cardiovascular system

Effect of age The slight but probably significant positive correlation between heart volume and age was of the same magnitude as has been shown earlier in healthy men (24) Owing to the probably more exact method of tomography larger hearts were also observed in older adults (6) In the present study however, age lost its significance when tested together with ECG_{total} and the correlation between age and heart volume was thus due to the increase with age of electrocardiographic deviations from the normal This may explain why an increase in heart volume with age was not observed in some studies (17, 20, 21) in which the subjects with abnormal or suspected abnormal findings in the exercise electrocardiogram were excluded and why an increase with age was observed in the studies mentioned above

As the stroke volume both at rest and during exercise decreases with rising age (5, 11) an unchanged heart volume with age indicates either a slight increase of the residual blood within the heart or a slight increase of the muscular volume The reported increase in heart weight with rising age in an autopsy material of males with no or only slight sclerosis of the coronary arteries (approx 50 g in 30 years) (13) roughly corresponds to the predicted volume changes due to decrease in stroke volume with age

Effect of electrocardiographic findings The mean increase in heart volume of 150 ml or 19 % in the cases with abnormal ECG_{total} may be due either to muscular hypertrophy or to dilatation of the heart The present study cannot decide which is the most probable but studies of the muscular weight in relation to heart volume in autopsy material of subjects with coronary heart diseases (9) would indicate that muscular hypertrophy is the most pronounced cause, except in the cases with the largest total heart volumes Approximately 150 g heavier hearts were also found in 50—50 year-old males with marked sclerosis of the coronary arteries compared with those having no or only slight sclerosis (13)

Effect of ST depressions The highly significant correlation between the total assessment of the electrocardiographic findings at rest, during and after exercise (ECG_{total}) and heart volume was shown to be due both to ST depressions and to ventricular ectopic beats ST depressions during or after the exercise test were

highly significant wheras ST depressions at rest were of probable significance This indictates that the classification of the ST segment in the present study was of significance even in otherwise healthy men aged 30—83 years

In patients with coronary heart disease and angina pectoris or myocardial infarction, larger heart volumes than in healthy males have been observed (10, 23), also in materials not including cases with incompensation or hypertension (8) These observations in subjects with coronary artery sclerosis and more marked ST depressions in the exercise electrocardiogram than found in apparently healthy men would strongly support the suggestion that the observed ST-depressions in the present material are sign of coronary insufficiency which might be the cause of the increase of the heart volume

Effect of ventricular ectopic beats Ventricular ectopic beats recorded in connection with exercise tests have not been found to influence the morbidity or mortality in coronary heart disease in follow-up studies (7, 27) Nor have they been found to be correlated to the degree of ST depression in the exercise electrocardiogram (1, 29) The presently observed and probably significant correlation between ventricular ectopic beats and the cardiovascular parameter, heart volume, should then be of interest From the present data it is not possible to state what is cause and what is effect The findings suggest, however, that ventricular ectopic beats in apparently healthy men are associated with cardiac factors and not related to any central nervous effects

Effect of heart rate at rest in supine and standing position A significant correlation between the heart volume and the heart rate at rest in the supine position, when consideration is paid to weight, has been observed earlier (16) In the present study the negative correlation between heart volume and heart rate in standing or supine position was lost when weight, blood volume and ECG_{total} were included as independent variables However, the increase in heart rate in standing position was still of probable significance This relationship is probably due to the fact that a large central blood volume would both cause a large heart volume and would tend to decrease the effect on heart rate of blood volume displacements in standing position It has been shown by Kjellberg et al (19) that variations in the pulmonary blood content lead to corresponding changes of the heart volume

Summary

The heart volume in prone position has been determined roentgenologically in 74 healthy men aged 30—83 years

The mean heart volume was 828 ml with a standard deviation of ± 19 4 % of the mean

By multiple regression analysis with the heart volume as dependent variable the residual standard deviation decreased to ± 12 0 % with the three significant independent variables weight, assessment of the electrocardiographic findings during the exercise test (ECG_{total}), and blood volume or total haemoglobin The only fourth variable of probable significance was either the arterial lactate concentration during exercise at heart rate 130 or the heart rate increase in standing position (HR_{st-sup}) All the variables except HR_{st-sup} had positive regression coefficients

Age was of probable significance when tested as single independent variable, but lost its significance when tested together with ECG_{total} The correlation between

age and heart volume was thus attributed to the increase with age of electrocardiographic deviations from the normal

The mean heart volume in the subjects with normal ECG_{total} was 760 ml at a mean weight of 73 kg The mean increase of heart volume in the cases with abnormal ECG_{total} was 150 ml or 19 per cent, with an increase of all heart diameters

Both the assessment of the ST segment during the exercise test and the ventricular ectopic beats were of significance for the heart volume Also the assessment of the ST segment and the total findings in the electrocardiogram at rest were of probable significance

Neither the systolic nor the diastolic arterial blood pressure at rest was of probable significance for the heart volume when the effect of age was corrected for

Acknowledgements

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Total Haemoglobin, Blood Volume and Haemoglobin Concentration at Rest and Circulatory Adaptation During Exercise in Relation to Some Anthropometric Data in Old Men Compared with Young Men[1]

By

T Strandell

In order to predict normal values for blood volume, total haemoglobin, red cell mass or plasma volume the observed values have been correlated to different body dimensions, such as weight, height and calculated body surface area (1, 14 16 24)

The influence of body composition and age on the blood volume have also been studied After effects of height and weight had been accounted for no significant correlation with somatotype was observed by Wennesland et al (30) However a significant negative correlation with subcutaneous fat thickness was found by Hicks *et al* (11) It has been claimed that blood volume is best predicted by total body water or lean body mass calculated from total body water (15 21) These observations on materials with variation in age between 19 and 65 years are not in accordance with the findings that total body water decreases with age 27 % between the ages 26 to 84 years (22) and that most studies show no changes in blood volume with rising age A constant blood volume up to 90 years of age has thus been found in males by plasma volume measurements (2) and by method, measuring the total haemoglobin (24) or the red cell mass (9, 26)

The blood volume is also influenced by the degree of physical training In athletes with high physical working capacity the dimensions of the cardiovascular system (heart volume and blood volume) and the measured value of its function (working intensity at heart rate 170 beats/min) were both found to be increased compared to normal men (17) High correlations between the three variables heart volume, blood volume and working intensity at heart rate 170 have been observed in mixed materials including children women ordinary men and athletes (13, 17)

The purpose of the present investigation was to study the relationships be

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Table II Height weight, body surface area (BSA) total haemoglobin (THb) haemoglobin concentration (Hb conc) blood volume (BV) heart volume (HV) and intensity of work at heart rate 130 beats/min (W_{130}) and at 170 beats/min (W_{170}) in 74 men aged 30—83 years *Mean values ± SD*

Age group (yrs)	No of individ.	Age (yrs)	Height (cm)	Weight (kg)	BSA (m^2)	THb (g)	Hb conc (g/100 ml)	BV (l)	HV (ml)	W_{130} (kpm/min)	W_{170} (kpm/min)
30–39	22	34.3 ± 2.5	176.3 ± 7.2	71.7 ± 7.9	1.89 ± 0.13	796 ± 118	13.56 ± 0.83	5.87 ± 0.77	768 ± 102	600 ± 149	960 ± 178
40–49	11	44.4 ± 2.7	175.6 ± 6.6	76.8 ± 9.8	1.93 ± 0.15	822 ± 139	13.15 ± 0.82	6.27 ± 1.12	846 ± 173	737 ± 143	1 109 ± 181
50–59	10	54.7 ± 3.0	172.9 ± 6.4	70.4 ± 9.1	1.84 ± 0.11	781 ± 119	12.98 ± 1.08	6.03 ± 0.89	805 ± 125	638 ± 218	1 003 ± 273
60–69	17	65.7 ± 2.9	174.4 ± 6.5	73.8 ± 10.5	1.89 ± 0.14	766 ± 101	13.38 ± 0.86	5.73 ± 0.67	867 ± 155	634 ± 149	1 008 ± 226
70–75	10	72.2 ± 1.6	173.3 ± 4.0	73.4 ± 9.6	1.87 ± 0.12	760 ± 117	13.31 ± 1.22	5.70 ± 0.59	834 ± 179	637 ± 146	[1]952 ± 171
80–83	4	81.3 ± 1.3	175.5 ± 8.3	72.5 ± 15.3	1.88 ± 0.21	774 ± 165	12.80 ± 0.67	6.02 ± 1.06	981 ± 335	655 ± 158	[2]850 ± 71
30–83	74	53.4 ± 16.6	174.9 ± 6.5	73.0 ± 9.4	1.89 ± 0.14	785 ± 118	13.30 ± 0.92	5.90 ± 0.82	828 ± 160	641 ± 160	[3]996 ± 205

[1] The number of individuals = 9
[2] The number of individuals = 2
[3] The number of individuals = 71

low n = 32) were obtained with the formula in the patients who had been given a larger amount than usual of pure CO (31 19 ml) and had higher values of total haemoglobin (body weight > 80 kg and patients with polycytaemia) Similarly significantly higher relative values (+ 2 2 % n = 13) were observed in the subjects who had lower values of total haemoglobin and had been given a smaller amount of pure CO (12 00—14 15 ml) (body weight < 40 kg and patients with anaemia) In cases in which the usual amount of CO (18 72 ml) had been given the standard error was ± 1 13 % of the mean value The error of the approximate formula of Linderholm could further be decreased by introducing empirical correction factors for barometric pressure and room temperature When the significant systematic error of the barometric pressure (753 ± 7 6 mm Hg mean ± SD) was taken into account the standard error decreased to ± 1 00 % and including also the significant error of the room temperature (21 6 ± 1 9 C) the standard error decreased to ± 0 86 % The modification of the approximate formula is given in table I The constant was increased by 1 % compared to the value given by Linderholm which includes the change due to exclusion of the rubber bag sampled 15 min after the supply of CO

Haemoglobin concentration

Haemoglobin concentration was determined spectrophotometrically in finger blood drawn after 10—30 min in the recumbent position 0 025 ml blood was haemolysed in 5 ml 0 04 % ammonium solution and the extinctions were read at 540 mμ The method was standardized by determinations of the oxygen capacity with the Van Slyke technique Duplicate determinations were used in all but three cases The first determination was generally performed 1—2 hours after the exercise test

Table I Approximate formula for calculation of total haemoglobin (THb, g)

$$THb = \frac{2.60 \cdot V_s \cdot F_{sCO} \cdot F_{O_2} \cdot k_{PB} \cdot k_T}{1{,}000 \cdot (F_{CO_{II}} - F_{CO_I})}$$

V_s	= volume of concentrated CO gas supplied to the system = 18.72 ml ATP, see text
F_{sCO}	= fraction of CO in the gas supplied to the system = 0.995
F_{O_2}	= fraction of O_2 in the second sampling rubber bag
F_{CO_I}	= fraction of CO in the first sampling rubber bag before the supply of CO
$F_{CO_{II}}$	= fraction of CO in the second sampling rubber bag, 30 min after supply of CO
k_{PB}	= correction factor for the barometric pressure. The slope of the factor on P_B was positive. At 760 mm Hg the factor was 1.000, for a change of ± 10 mm Hg it changed by ± 0.013%
k_T	= correction factor for the room temperature. The slope of the factor on temperature was negative. At 21.6° C the factor was 1.000, for a change of ∓ 1° C it changed by ± 0.0030

tween total haemoglobin, blood volume, haemoglobin concentration and working intensity at heart rate 130 and several other parameters such as age, electrocardiographic findings, body size and heart volume in a material of healthy men of different ages

Material

Seventy four healthy men aged 30—83 years were studied. The selection of these men was described in a previous paper (29) in which also some aspects of the material were discussed

Methods

The methods used but not described in the present study, including statistical calculations, were discussed in the previous paper (29)

Total haemoglobin

The total haemoglobin was determined by the alveolar CO method (23) with some modifications (19, 20, 31). The method is based upon rebreathing in a closed circuit and measuring the fraction of carbon monoxide in the system before and after the addition of a known volume of pure CO. The volume of the rebreathing apparatus was measured by helium dilution and found to be approximately 3.1. The volumes of the rubber bag and the patients' lungs after exhalation were approximated to 5 l and 1.5 l respectively. Variations in these volumes, however, influence the calculated value of total haemoglobin rather little, e.g. if the volume of the rubber bag or the patient's lungs is 1 litre lower than the predicted values, the total haemoglobin would be underestimated by approximately 0.5 % and 0.3 % respectively. The procedure, analysis and calculations were the same as previously described by Wiklander (31) and Linderholm (18), except that only one rubber bag was collected and analyzed 30 minutes after the supply of CO into the system

Duplicate determinations were used in all but two cases. The coefficient of variation for a single determination was 6.6 % computed from 72 double determinations. In most cases a third determination was made if the two first values differed more than 10 % and the mean value was calculated from the three determinations. The standard error of the values of total haemoglobin (mean of at least two) given below was thus less than 4.6 %

In order to decrease the time spent on the calculation of total haemoglobin a simplified approximate formula was constructed by Linderholm (unpublished observation). In connection with the present investigation, this formula was compared with the original calculations in 200 determinations of total haemoglobin in 100 randomly selected patients sent to the laboratory. The standard deviation for the difference between the value derived from the approximative formula of Linderholm and that from the original calculations was then ± 2.00 % of the mean value (n = 200). It was observed that significantly lower relative values (— 2.8 % after correction for barometric pressure and temperature, see be

minations The standard error of the value given below (mean of at least two) was thus less than 5 3 %

Exercise test

This consisted of stepwise increased work loads (every sixth minute) on a bicycle ergo meter in sitting position starting at 300 km/min as is usual in this laboratory (25) Heart rate was determined from electrocardiographic recordings The intensity of work at heart rate 130 (W_{130} kpm/min) was determined by intrapolation in three cases by a short extrapolation (maximal heart rates 117–126 beats/min) W_{170} was determined in a similar way In three cases no value for W_{170} could be obtained owing to low maximal heart rates during exercise W_{130} was therefore used instead of W_{170} in the multiple regression analysis A more complete description of the test was given in previous reports (28 29) W_{130} and W_{170} are estimates of the oxygen pulse during exercise at these heart rates Besides the mechanical efficiency during exercise they are dependent both on the stroke volume and on the arteriovenous oxygen difference (25) In the present study they were used as functional parameters for describing the circulatory adaptation during exercise

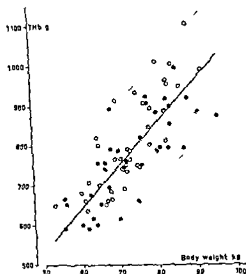


Fig 1 Total haemoglobin in relation to body weight in 74 healthy men aged 30–83 years Open circles denote subjects aged 30–35 years filled circles denote subjects aged 56–83 years Regression line (section 1 table III) ± 2 SD

Results

The mean values in the different decades of some of the measured parameters are given in table II

Total haemoglobin as dependent variable

Some of the relationships that were obtained with total haemoglobin as the dependent variable in regression and multiple regression analysis are given in table III

The lowest residual standard deviation was obtained with body surface area as the independent variable followed by weight (fig 1) heart volume height, W_{130} and the haemoglobin concentration (section 1) Besides the correlations listed in table III the total haemoglobin was also correlated to 2—6 min heart rate increase at 600 kpm/min, (r = — 0 40***) and heart rate at rest supine (r = - 0 24*)

As the body surface area was calculated from the fixed height weight formula of Du Bois, the independent variables, weight and height, were used instead in the multiple regression studies These two independent variables (section 2, table III) gave the same residual standard deviation as body surface area alone When combining two independent variables it was noted that W_{130} was insignificant ($P > 0.05$) together with weight W_{130} was of probable significance together with heart volume but the residual standard deviation was then greater than with weight alone (± 11 2 %) None of the assessments of the ECG were of probable significance when tested alone or in combination with weight Nor were low

Table III Total haemoglobin (y, g) in relation to body surface area (BSA, m²), weight (kg), heart volume (HV, ml), height (cm), W_{130} (kpm/min), haemoglobin concentration (Hb conc, g/100 ml) and age (yrs) in 74 healthy men aged 30—83 years. Mean value ± SD for total haemoglobin = 785 ± 118 g or ± 15.0 % of the mean. r = correlation coefficient, R = multiple correlation coefficient. The section number indicates the number of indifferent variables

Section	Independent variable	Regression equation	Residual SD g	Residual SD % of mean	b/εb	r	R
1	BSA	$y=-510+687x$	70	8.9	11.67***	0.809	
	Weight	$y=74+9.75x$	74	9.4	10.64***	0.782	
	HV	$y=394+0.473x$	91	11.6	7.14***	0.644	
	Height	$y=-1,166+11.16x$	94	11.9	6.58***	0.613	
	W_{130}	$y=552+0.36x$	103	13.1	4.81***	0.493	
	Hb conc	$y=50+55.2x$	107	13.6	4.08***	0.433	
2	Weight (x_1)	$y=-609+7.96x_1+4.65x_2$	70	8.9	7.60***		0.810
	Height (x_2)				3.03**		
3	Weight (x_1)	$y=-1,106+6.59x_1+5.60x_2+32.3x_3$	65	8.2	6.36***		0.844
	Height (x_2)				3.91***		
	Hb conc (x_3)				3.68***		
	Weight (x_1)	$y=-595+6.32x_1+4.58x_2+0.142x_3$	69	8.7	4.87***		0.822
	Height (x_2)				3.06**		
	HV (x_3)				2.06*		
4	Weight (x_1)	$y=-1,126+5.59x_1+4.54x_2+34.7x_3+0.169x_4$	62	7.9	3.63***		0.860
	Height (x_2)				4.07***		
	Hb conc (x_3)				4.10***		
	HV (x_4)				2.69**		
5	Weight (x_1)	$y=-918+4.41x_1+4.82x_2+31.2x_3+0.219x_4-1.10x_5$	60	7.7	3.63***		0.870
	Height (x_2)				3.50***		
	Hb conc (x_3)				3.74***		
	HV (x_4)				3.38**		
	Age (x_5)				−2.25*		

and showed systematically higher values ($P < 0.05$) than the second + 0.20 ± 0.73 g/100 ml (mean ± SD, n = 71). This systematic error, however, was too small to influence significantly the results in the present study. The random coefficient of variation for a single determination was 3.9 % and for the double determination that 2.7 %, including biological as well as methodological errors.

Blood volume

The blood volume was calculated from the values of the total haemoglobin and the haemoglobin concentration in finger blood. No correction was made for the generally accepted difference between the *haematocrit in finger* blood and that of the total blood volume (+ 9 %, see Gregersen et al (7)). The coefficient of variation for a single determination was 7.5 % computed from 72 double deter-

independent variable Together with heart volume age was a highly significant variable The probable significance of age in section 5 table III can thus entirely be ascribed to the fact that the total haemoglobin was better predicted when the increase of the heart volume with age was accounted for

Blood volume as dependent variable

Some of the relationships that were obtained with regression and multiple regression analysis are given in table IV

The lowest residual standard deviation was obtained with body surface area as the independent variable followed by weight (fig 2) height heart volume and W_{130} (section 1) Besides the correlations listed in table IV the blood volume was also correlated to 2—6 min heart rate increase at 600 kpm/min ($r = -0.37^{**}$) and heart rate at rest supine ($r = -0.28^{*}$)

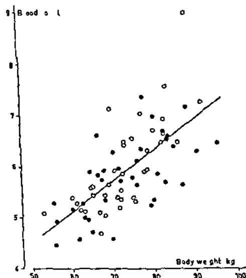


Fig 2 Blood volume in relation to body weight in 74 healthy men aged 30—83 years Open circle denote subjects aged 30—55 years filled circles denote subjects aged 56 83 years Regression line (section 1 table IV) ± 2 SD

As for total haemoglobin the independent variables weight and height were used instead of body surface area in the multiple regressions (section 2 table IV) W_{130} lost its significance when combined with weight ($P>0.1$) None of the assessments of the ECG were of probable significance when tested alone or in combination with age or weight Nor were log arterial lactate concentration at heart rate 130 or the anamnestic degree of physical activity of probable significance

Both the haemoglobin concentration and the heart volume were significant independent variables when combined with weight and height (sections 3 and 4 table IV) Haemoglobin concentration however was insignificant when tested as single variable ($r = 0.04$) It is to be noted that the blood volume was not measured independently but was calculated as the quotient between total haemoglobin and haemoglobin concentration Thus at least part of the correlation with haemoglobin concentration was due to this fact

With five independent variables the residual standard deviation decreased to ± 7 8 % of the mean (section 5 table IV) compared to the original standard deviation of ± 13 9 % Age was the probably significant fifth variable as for total haemoglobin and this was due to the correlation between age and heart volume Age was thus not of probable significance when tested alone or in combination with weight height or haemoglobin concentration but significant when combined with heart volume

Haemoglobin concentration as dependent variable

Some of the relationships that were obtained with haemoglobin concentration

Table II Blood volume (y, l) in relation to body surface area (BSA, m²), weight (kg), height (cm), heart volume (HV, ml), W_{130} (kpm/min), haemoglobin concentration (Hb conc, g/100 ml) and age (yrs) in 74 healthy men aged 30—83 years Mean value ± SD for blood volume = 5.90 ± 0.821 or ± 13.9 % of the mean Other symbols as in table III

Section	Independent variable	Regression equation	Residual SD l	Residual SD % of mean	b/εb	r	R
1	BSA	$y = -2.71 + 4.57x$	0.52	8.8	10.46***	0.777	
	Weight	$y = 1.50 + 0.0603x$	0.59	10.0	8.26***	0.698	
	Height	$y = -8.78 + 0.0840x$	0.61	10.4	7.57***	0.666	
	HV	$y = 3.22 + 0.00324x$	0.63	10.7	7.01***	0.637	
	W_{130}	$y = 4.28 + 0.00253x$	0.71	12.1	4.82***	0.494	
2	Weight (x_1) Height (x_2)	$y = -5.92 + 0.0409x_1 + 0.0506x_2$	0.53	8.9	5.21*** 4.41***		0.773
3	Weight (x_1) Height (x_2) Hb conc (x_3)	$y = -2.65 + 0.0499x_1 + 0.0442x_2 - 0.213x_3$	0.49	8.4	6.23*** 4.03*** -3.16**		0.805
	Weight (x_1) Height (x_2) HV (x_3)	$y = -5.78 + 0.0241x_1 + 0.0499x_2 + 0.00146x_3$	0.50	8.5	2.54* 4.57*** 2.89**		0.800
4	Weight (x_1) Height (x_2) Hb conc (x_3) HV (x_4)	$y = -2.80 + 0.0341x_1 + 0.0442x_2 - 0.194x_3 + 0.00131x_4$	0.47	8.0	3.56*** 4.20*** -3.01** 2.73**		0.8[illegible]
5	Weight (x_1) Height (x_2) Hb conc. (x_3) HV (x_4) Age (x_5)	$y = -1.16 + 0.0330x_1 + 0.0381x_2 - 0.222x_3 + 0.00170x_4 - 0.0087x_5$	0.46	7.8	3.56*** 3.62*** -3.48*** 3.44*** -2.34*		0.840

arterial lactate concentration at heart rate 130 or the anamnestic degree of physical activity of probable significance

Combined with weight and height, both haemoglobin concentration and heart volume were significant independent variables (section 3, and 4, table III)

Age was the only variable tested that was of probable significance together with weight, haemoglobin concentration and heart volume (section 5, table III) With these five best variables the residual standard deviation decreased to ± 7.7 % of the mean compared to the original standard deviation of ± 15.0 %

The probable significance of age as the fifth independent variable needs some further comment Age as single independent variable was not significant ($P > 0.2$) nor in combination with height or haemoglobin concentration Age was of probable significance together with weight (b = — 1.2) but this significance was lost when height was combined as a third

Table VI Intensity of work at heart rate 130 (W_{130} kpm/min) in relation to heart rate in standing position (HR_{St} beats/min) heart rate at rest supine (HR_{Sup} beats/min), blood volume (BV l) total haemoglobin (THb g), weight (kg) heart volume (HV ml) height (cm) and anamnestic degree of physical activity (phys act scale 1—3) in 74 healthy men aged 30—83 years Mean value ± SD for W_{130} = 641 ± 160 or ± 24 9 % of the mean Other symbols as in table III The number of subjects = 70 in section 3

Section	Independent variable		Regression equation	Residual SD kpm/min	Residual SD % of mean	b/sb	r	R
1	HR_{St}		y=1 169−6 53x	131	20 4	−6 02***	0 578	
	HR_{Sup}		y=1 176 −8 05x	139	21 7	−4 87***	0 498	
	BV		y= 72+96 5x	140	21 8	4 82***	0 494	
	THb		y=117+0 6f8x	140	21 8	4 81***	0 493	
	Weight		y=51+8 08x	141	22 0	4 51***	0 476	
	HV		y=250+0 472x	141	22 0	4 58***	0 47a	
	Height		y = − 1 030+9 56x	148	23 1	3 57***	0 387	
2	HR_{St}	(x_1)	y=614−5 93x_1+6 95x_2	114	17 8	−6 23***		0 708
	Weight	(x_2)				4 87***		
	HR_{St}	(x_1)	y =676−5 72x_1+0 546x_2	115	18 0	−5 90***		0 701
	THb	(x_2)				4 69***		
	HR_{Sup}	(x_1)	y=598−7 12x_1+7 06x_2	123	19 2	−4 82***		0 648
	Weight	(x_2)				4 .8***		
	THb	(x_1)	y=80+0 453x_1+0 268x_2	137	21 3	2 43*		0 534
	HV	(x_2)				2 06*		
3	HR_{St}	(x_1)	y=518−5 49x +6 12x_2+67x_3	109	17 0	−5 66***		0 737
	Weight	(x_2)				4 33***		
	Phys act	(x_3)				3 21**		

Intensity of work at heart rate 130 (W_{130}) as dependent variable

Some of the relationships that were obtained with W_{130} as the dependent variable in regression and multiple regression analysis are given in table VI

The lowest residual standard deviation was obtained with heart rate in standing position (HR_{St}) as the independent variable followed by heart rate in supine position (HR_{Sup}) blood volume total haemoglobin weight heart volume and height (section 1 table VI) Besides the correlations listed in table VI W_{130} was also correlated to anamnestic degree of physical activity (r = 0 41*** n = 70) and heart rate increase in standing position (r = − 0 37**) W_{130} was not significantly correlated to log lactate at heart rate 130 (r = 0 25, n = 54), the 2—6 min heart rate increase at heart rate 130 (r = 0 09) or age (r = 0 03)

When the regression computations were performed with two independent variables the lowest residual standard deviation was obtained with HR_{St} or HR_{Sup} as one of them and weight, total haemoglobin or blood volume as the other (section 2, table VI) Heart volume was of probable significance when tested with total haemoglobin but not when tested as the third variable together with total haemo-

Table V Haemoglobin concentration (y, Hb conc , g/100 ml) in relation to total haemoglobin (THb, g) weight (kg), height (cm), blood volume (BV, l) and age (yrs) in 74 healthy men aged 30—83 years Mean value ± SD for Hb conc = 13 3±0 92 g/100 ml or ± 6 9 % of the mean Other symbols as in table III

Section	Independent variable	Regression equation	Residual SD g/100 ml	Residual SD % of mean	b/εb	r	R
1	THb	$y=10\ 6+0\ 0034x$	0 84	6 3	4 08***	0 433	
	Weight	$y=11\ 0+0\ 031x$	0 88	6 7	2 86**	0 319	
2	THb (x_1) Height (x_2)	$y=18\ 4+0\ 0052x_1-0\ 0517x_2$	0 80	6 0	5 14*** −2 87**		0 591
	Weight (x_1) BV (x_2)	$y=11\ 9+0\ 066x_1-0\ 59x_2$	0 82	6.2	4 70*** −3 58***		0 4[illegible]9
	Weight (x_1) Height (x_2)	$y=15\ 4+0\ 043x_1-0\ 030x_2$	0 87	6 5	3.25** −1 54		0 361
3	Weight (x_1) BV (x_2) Age (x_3)	$y=12\ 6+0\ 070x_1-0\ 63x_2-0\ 012x_3$	0 80	6 0	5 03*** −3 91*** −2 05*		0 53[illegible]

as the dependent variable in multiple regression analysis are given in table V

The lowest residual standard deviation was obtained with total haemoglobin as he independent variable, followed by weight (section 1, table V) According to the regression coefficients an increase in weight of 10 kg in the material or increase in total haemoglobin of 100 g corresponded to an increase in haemoglobin concentration of 0 3 g/100 ml Neither age (r = — 0 15), height (0 04) nor blood volume (— 0 04) were of probable significance for the haemoglobin concentration as single variables

When the regression computations were performed with two independent variables, the lowest residual standard deviation was obtained with total haemoglobin and height as these variables followed by weight and blood volume (section 2, table V) It has to be repeated however that blood volume was not measured independently but was calculated from the values of total haemoglobin and haemoglobin concentration When weight and height were tested together, the negative regression on height did not reach the level of probable significance

Age was not even of probable significance when tested alone or in combination with any of the other variables When tested together with both weight and blood volume, however, age became probably significant According to the regression coefficient an increase in age of 50 years corresponded to an increase in haemoglobin concentration of 0 6 g/100ml

With the best two or three independent variables the residual standard deviation of the haemoglobin concentration only decreased to ± 6 0 % of the mean, compared to the original standard deviation of ± 6 9 % The relationships studied above are thus of no practical importance for predicting haemoglobin concentration in healthy men, but may be of theoretical interest

lean body mass decline with age whereas blood volume remain unchanged However, it seems as if a combination of body weight and height as independent variables for predicting blood volume will account equally well for the variance due to differences in body size between individuals as for most of the variance due to variations in body composition

Relation to age The unchanged values for blood volume and total haemoglobin with rising age in the present study are in accordance with most previous reports (2 9 24, 26, 30) Possible reasons why some previous reports have shown a change of the blood volume with age may have been technical errors or the selection of the materials as suggested by Yiengst et al (33)

Relation to heart volume The correlation with heart volume in the present material after effects of weight and height are taken into account might be ascribed to varying degree of physical training or possibly to dispositional variations in the relationship between weight height and the size of the cardiovascular system (compare the discussion in the previous paper (29)

Relation to haemoglobin concentration At normal survival time of the red blood corpuscles the haemoglobin concentration is dependent on the haematopoietic activity The blood volume is adapted to the size of the vascular system and normally not related to the haemoglobin concentration Total haemoglobin on the other hand is dependent both on the size of the vascular system and on the haematopoietic activity In the present study total haemoglobin was primarily related to haemoglobin concentration but blood volume was not When consideration was paid also to weight and height however, there was a significant relationship between blood volume and haemoglobin concentration This was probably because total haemoglobin was well predicted by weight and height, and at a fixed value of total haemoglobin the blood volume will vary with the haemoglobin concentration

Haemoglobin concentration as dependent variable

Relation to age A slight but significant decrease of the haemoglobin concentration with rising age has sometimes been observed in large population studies of males (8), whereas others have shown unchanged values (5, 12) The different findings seem to be explained by the selection of the materials and by the observation that poor diet was the main contributory factor in low values of haemoglobin concentration in old males (12) A significant negative correlation between haemoglobin concentration in normal old males and the intake of protein and iron in the food has also been observed (5) In part the relationship between body size and haemoglobin concentration may also have contributed

In the present study there was no primary correlation between haemoglobin concentration age However, by multiple regression it was shown that age was of probable significance for haemoglobin concentration at constant weight and blood volume but the effect was small

Relation to body size and total haemoglobin The increase in haemoglobin concentration with increasing body weight in the present study is in accordance with the findings of Wintrobe (32) there being no correlation of probable significance with height as single variable However, the negative correlation with height when

globin and HR_{st} or HR_{Sup} Log lactate at heart rate 130 was of probable significance (b = 260, n = 54) when tested together with anamnestic degree of physical activity but not when tested together with weight or HR_{st}

None of the different electrocardiographic assessments during the exercise test were of probable significance as single independent variables The assessment of the ST-segment (ECG_{ST}), however, was of probable significance (b = 27) when tested together with blood volume When heart volume was combined as the third independent variable both ECG_{ST} ($b/_{sb}$ = 1 1) and heart volume ($b/_{sb}$ = 1 8) lost their probable significance The slightly increased W_{130} in the subjects with abnormal ECG_{ST} was thus partly connected with their slightly increased heart volumes, although neither heart volume nor ECG_{ST} reached the level of probable significance when tested together

The anamnestic degree of physical activity was significant when tested with HR_{st} and weight (section 3, table VI) With these three variables the residual standard deviation decreased to ± 17 0% of the mean compared to the original standard deviation of ± 24 9 %

The almost identical correlation coefficients with heart volume and total haemoglobin for W_{130} and W_{170} have already been mentioned in the previous paper (29) The correlation coefficients with HR_{st} (—0 56*** and —0 33** respectively, n = 71) and HR_{sup} (—0 46*** and —0 25*) were somewhat lower for W_{170}, but the differences were not of probable significance (tested after conversion to z), nor were the differences in regression coefficients The regression of W_{170} (y) on total haemoglobin (x) in the 71 subjects when W_{170} could be estimated was $y = 360 + 0\,814x$, SD = 182 kpm/min, r = 0 47 The regression of W_{170} (y) on heart volume (x) was y = 437 − 0 661x, SD = 183 kpm/min, r = 0 47, n = 71

Discussion

Total haemoglobin and blood volume as dependent variables

Relation to body size The variations in total haemoglobin and blood volume in the present material are in accordance with previous reports (1, 14, 16, 24) as are the variances after consideration was paid to weight and height

Effect of altered body composition with age Marked changes in body composition occur with rising age, among other things a decrease of total body water (22) This decrease of total body water with age should be of significance in the present study, as it has been claimed that blood volume is best predicted by total body water or lean body mass calculated from total body water (15, 21) The extremely low residual standard deviations in these studies, ± 2 — 2 5 % of the mean values, would indicate that blood volume was only correlated to lean body mass and not to fat mass However, other and more extensive reports (3, 14, 16, 27) have shown that also fat mass was significantly correlated to blood volume and that the prediction of blood volume from total body water lean body mass or fat mass, alone or in combination, was equal to or only slightly better than the prediction from height and weight combined In these last studies lean body mass was calculated both from total body water and after determination of body density

If total body water or lean body mass are used for prediction of blood volume, age should be a significant second independent [illegible]ariable as total body water and

bles had positive regression coefficients Neither age nor electrocardiographic findings during the exercise test were of probable significance as single variables

The mean blood volume was 5 90 l with a standard deviation of ± 13 9 % of the mean With blood volume as dependent variable the lowest residual standard deviation (± 8 0 % of the mean) was obtained with the same four independent variables as for total haemoglobin, but the regression coefficient for haemoglobin concentration was negative Haemoglobin concentration was not of probable significance when tested alone Neither age nor electrocardiographic findings were of probable significance

The mean haemoglobin concentration was 13 3 g/100 ml with a standard deviation of ± 6 9 % of the mean The haemoglobin concentration was positively and significantly related to total haemoglobin and weight as single independent variables Height was significant with negative regression coefficient when tested together with total haemoglobin but not significant as single variable Age was not even of probable significance as single variable but taking the effects of weight and blood volume into account, age was of probable significance with negative regression coefficient With two or three independent variables the residual standard deviation only decreased to ± 6 0 %

The mean W_{130} was 641 kpm/min with a standard deviation of ± 24 9 % of the mean With W_{130} as dependent variable the lowest residual standard deviation (± 17 0 % of the mean) was obtained with the three independent variables heart rate at rest in standing position weight and anamnestic degree of physical activity Neither age nor electrocardiographic findings were of probable significance as single variables

Acknowledgements

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consideration was paid also to total haemoglobin or weight agrees with the observation of Wennesland et al (30) that the haematocrits of short, heavy men tended to be slightly higher than those of tall, thin men The reason for this relation to body size, which is too small to be of practical interest, is not clear It might be due to possible differences in the relationship between body haematocrit and venous haematocrit

Within certain limits the blood volume remains rather constant in spite of variations in haemoglobin concentration Moderate variations in haemoglobin concentration induced by variations in the haematopoetic activity will then induce corresponding changes in total haemoglobin, and this may explain the positive correlation between these two variables

W_{130} AS DEPENDENT VARIABLE

Relation to heart rate at rest The highly significant negative relation between W_{130} and heart rate at rest standing or supine is to be expected, as these values correspond to the starting level for heart rate during exercise Furthermore, both the heart rates at rest and those during exercise are related to the stroke volume and therefore correlated to each other

Relation to body size The positive relationships between W_{130} and weight and to a smaller extent between W_{130} and height are in accordance with the findings in young conscripts (10) However, in a study of 40—50 year-old men (4) no such obvious relation was observed

Relation to total haemoglobin and heart volume The regression of W_{130} on heart volume was not significantly different from the regression found by Hellstrom (10) on conscripts but the slope was flatter ($P < 0\,001$) than that of the values reported by Holmgren et al (13), as was the slope of the regression of W_{130} on total haemoglobin These differences, however, were only due to the low correlation coefficients in the present material When calculating the regression lines with W_{130} as the independent instead of as the dependent variable the regressions lines in the present study thus rotated 35°—40° As the regression lines of Holmgren et al were fairly unchanged there was still a significant difference in slope between the materials, but now in opposite direction

Relation to age W_{130}, like W_{130}, is dependent both on the stroke volume and on the arteriovenous oxygen difference during exercise at that heart rate (25) Both factors change with age (6) but the decline in stroke volume seemed to correspond to the increase in arteriovenous oxygen difference Neither W_{130} nor W_{130} was thus significantly influenced by age in the present study The similarity with other reports in this respect has been discussed in a previous paper (28)

Summary

The total haemoglobin and the blood volume were determined by the alveolar CO method and the intensity of work at heart rate 130 (W_{130}) was determined during sitting bicycle exercise in 74 healthy men aged 30—83 years

The mean total haemoglobin was 785 g with a standard deviation of ± 15 0 % of the mean By multiple regression analysis with total haemoglobin as dependent variable the lowest residual standard deviation (± 7 9 % of the mean) was obtained with the four independent variables body weight height, haemoglobin concentration and heart volume All vari

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Catheterization of the Left Adrenal Vein for Contrast Injection and Steroid Analysis in a Case of Conn's Syndrome

By

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Conn s syndrome is characterized by hypertension signs and symptoms of potassium depletion and increased aldosterone production on the basis of an aldosterone producing adrenal adenoma (12) As pointed out in recently published reviews (12 21, 22), these adrenal adenomas, often referred to as aldosteromas or aldosteronomas (5 11), are usually so small that they cannot be shown by common roentgenological methods including general view of the abdomen, presacral air insufflation and aortography Bucht (7) has recently described a method for percutaneous catheterization of the left adrenal vein, and this method has now been used in a case of primary aldosteronism for the localization of the adrenal cortical adenoma and for the determination of the hormone secretion into the adrenal vein In addition water and electrolytes were determined in muscle biopsy specimens according to procedures recently described by Bergstrom (3)

Submitted for publication January 28 1964

Case report

A 35 year-old housewife was referred to the kidney unit St. Erik s Hospital in Sept 1962 because of pre umed acute nephritis Her family history revealed nothing of importance Earlier she had been completely healthy and had given birth to 3 normal children in Aug 1961 legal abortion on social psychiatric grounds was performed in the fourth month of pregnancy the patient then was reported to have a normal blood pressure of 130/90 and there was no proteinuria In Feb 1962 he was operated upon because of numerous gallstones she was then found to have moderately elevated blood pressure (160/110) but showed no proteinuria no electrolytes were determined at that time After operation she was treated by her general practitioner with a thiazide diuretic (Bendroflumetiazid 2 5 mg × 2—3),

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TABLE III Results of kidney function test performed before operation

Urinary volume	1 900—2 300 ml/24 hrs
Proteinuria	Trace amounts
Urinary pH	
Ordinary morning specimen	7 0
After NH Cl	6 9
Max osm after pitressin	460 mmol/l
Urinary sediment	Normal
Urine culture	No growth
Clearance	
Creatinine	97 ml/min
PAH	437 ml/min

TABLE IV Urinary excretion of 17 ketosteroid, (17 KS) 17 ketogenic steroids (17 KGS) and aldosterone

	17 KS (mg/24 hrs)	17 KGS (mg/24 hrs)	Aldosterone (µg/24 hrs)
Before op	2—3	14—21	77—107
10 days after op	2	8	4 8
12 days after op	0	3	3 7
13 days after op	1	9	1 4
3 months after op	7	14	1 1
Normal range	3—13	8—20	2—15

and the urinary pH was determined about 14 hours later

Catheterization of the left adrenal vein was performed in the following manner (7) A yellow Ödman catheter was introduced by the Seldinger technique into the right femoral vein under local anaesthesia The tip was placed in the left renal vein under TV-control It was slightly withdrawn and a Seldinger guide was introduced through the catheter into the left adrenal vein The original catheter was withdrawn and a thin polythene catheter was introduced into the adrenal vein via the guide which was then also removed The adrenal veins were visualized by injection of 2 ml 50 % Urografin® into the adrenal vein and simultaneous cinematographic exposure of a series of X ray pictures After injection of 25 mg heparin via the catheter and 50 mg heparin into a peripheral vein blood was collected from the catheter for the determination of steroid hormones The blood was allowed to flow spontaneously from the catheter in periods varying between 3 and 8 minutes The blood was instantly centrifuged and the plasma was separated and stored deep-frozen before analyses were made

Aldosterone in adrenal vein blood and urine was determined using a double-labelling isotope dilution technique essentially according to Kliman and Peterson (23) This

TABLE V Aldosterone secretion as measured by retrograde catheterization of the left adrenal vein

	µg/ml plasma	µg/min	µg/24 hrs
Normal I	0 013	0 034	50
Normal II	0 043	0 054	78
Patient	0 780	1 56	2 246

TABLE VI Cortisol secretion as measured by retrograde catheterization of the left adrenal vein No correction has been made for the systemic cortisol level amounting to 0 15—0 25 µg/ml

	µg/ml plasma	µg/min	mg/24 hrs
Normal	5 6	14 7	21 1
Patient	13 3	26 6	38 3

procedure does not permit the determination of aldosterone in peripheral plasma Cortisol in plasma was determined according to Peterson et al (33) urinary 17 ketogenic steroids according to Appleby et al (1)

TABLE I Plasma electrolytes and blood pH

	Before op	12 days after op
Na (mEq/l)	150	140
K (mEq/l)	2 1	4,4
Cl (mEq/l)	99	101
HCO_3 (mM/l)	35	25
pH	7 50	7 42

TABLE II Water and electrolytes in muscle tissue expressed per 100 g fat free solids

	Before op	12 days after op	Normal range[1]
H_2O (ml)	390	357	305 – 384
Cl space (ml)	143	77	40 – 130
K (mEq)	32 4	47 7	40 8 – 48 6
Na (mEq)	30 6	11 6	7 4 – 19 6
Cl (mEq)	15 8	8 8	4 4 – 15 7
P (mM)	29 9	30 9	27 3 – 31 7
Na_x[2]	9 2	0 9	−0 6 – 3 0
K/P	1 08	1 54	1 37 – 1 65
Na_x/P	0 31	0 03	−0 02 – 0 10

[1] As published by Bergstrom (3) using *the same* technique

[2] Na_x = excess sodium i e sodium not accounted for in the chloride space

peroral potassium and reserpine (Serpasil® 0 25 mg × 2) In July 1962, she experienced a sore throat and on examination by her family doctor she was found to have a blood pressure of 210/110 and moderate proteinuria, no casts were found She was treated with antibiotics but as her proteinuria persisted she was referred to the kidney unit

On admission she complained of general fatigue and polydipsia, but had otherwise no complaints Physical examination revealed a 33 year old healthy looking woman There were no signs of Cushing s syndrome and no abnormal pigmentation, hair growth was normal Physical examination of the heart showed normal conditions Blood pressure varied between 210/110 and 165/120 Examination of eye grounds revealed retinal changes corresponding to Keith Wagener I There were no objective signs of muscular weekness, and tendon reflexes as examined routinely were normal

Laboratory methods

Sodium and potassium in blood were determined in deproteinized, heparinized plasma using an Eppendorf flame photometer (4) The CO_2 content was determined by the van Slyke method and the pH in arterial whole blood was measured with a glass electrode at + 37° C Total exchangeable potassium (K_e) was determined by isotope dilution 150 uC K^{42} was given intravenously Four urine samples were collected between 22 and 26 hours after the injection and the K^{42} activity was measured with a G M tube K_e was calculated by conventional equations (16)

Muscle tissue was obtained from m quadriceps femoris by needle biopsy and analyzed for sodium, potassium, chloride and phosphorus by neutron activation analysis Water content was determined by weighing before and after drying and fat was extracted with petroleum ether The chloride space was calculated from the muscle and plasma chloride content and was used as a measure of the amount of extracellular fluid in muscle tissue *(20, 26)* Excess sodium i e the amount of sodium not accounted for in the chloride space (i e intracellular sodium) was calculated by subtraction of the amount of extracellular from the total muscle sodium The sampling and analytical methods and the methods of calculation have been described and discussed by Bergstrom (3)

Endogenous creatinine clearance and PAH clearance were determined by routine procedures For assessment of urinary acidification ability ammonium chloride 0 1 g per kg body weight was given in three doses

with two normal subjects plasma from the *left adrenal vein of the patient* showed a markedly high aldosterone concentration (table V) and also a comparatively high cortisol level (table VI) In peripheral blood cortisol varied within normal limits with the highest value (13 μg/100 ml) at 6 a m and the lowest value (5 μg) at midnight

The general X ray view of the abdomen as made routinely was normal However, adrenal vein catheterization with phlebography revealed a golf ball sized rounded structure penetrated by irregular coiled vessels within the suprarenal region (fig 1) This finding was confirmed at the subsequent aortography, which showed — although less distinctly — a tumour within the same area

Clinical course

Pre-operatively the patient was treated with spironolactone (Aldacton© 100 mg 4 times daily for 10 days) and concomitantly potassium chloride (6 g daily) In connection with the operation 875 mg Solu Cortef® was given intravenously during 6 days thereafter no steroid therapy was given

As the localization of the tumour had been established before operation the trans peritoneal approach was used The abdomen was opened with a left sided paramedian incision from the costal arcus passing down the umbilicus The colon transversum and the left flexura were mobilized and pushed downwards The parietal peritoneum was divided from the attachment of flexura lienalis coli up to cardia and the stomach spleen pancreas together with the dorsal wall of bursa omentalis were folded up to the right In this way very good access was obtained to the left renal suprarenal region with the adrenal lying in the middle of the operation field On the front side of the adrenal there was a walnut sized rounded blu sh tumour that could be enucleated easily from the normal adrenal tissue which was left intact It was also possible to palpate the right adrenal which was normal There were no signs of metastases locally or in the liver

Microscopic examination (Dr Stig Olsson) showed a capsulated adenoma with lipoid rich cells of varying size It was not possible to decide whether the cells had originated from the zona glomerulosa or from any of the inner zones of the adrenal cortex There were no signs of malignancy On incubation the adenoma produced considerable amounts of aldosterone (1 36 μg/g tissue/hour), and in addition rather large quantities of cortisol (5 95 μg/g tissue/hour)

The post-operative course was *uneventful* and the patient left the hospital in a good condition after 14 days About 12 days post operatively plasma electrolytes blood pH and the muscle electrolytes were normal, and furthermore, blood pressure had become normal Immediately after operation aldos terone excretion was below the lower limit of normal variation where is urinary 17 ketogenic steroids were slightly decreased Three months after operation blood pressure was 145/90 plasma electrolytes were normal as was urinary excretion of both 17 keto-steroids and 17 ketogenic steroids, urinary aldosterone still was slightly subnormal The patient felt well and worked normally

Discussion

The patient here described constituted a typical case of Conn s syndrome with regard to clinical as well as laboratory findings Thus there was arterial hyper tension hypokalaemia slight hyperna traemia metabolic alkalosis, and pitres sinresistant polyuria in combination with markedly elevated aldosterone produc tion The important question was localization of the aldosterone producing tumour This question could be satis-factorily answered using retrograde ad renal vein catheterization which made possible both the visualization of the tumour by X ray and the demonstration of a high aldosterone secretion rate in the left adrenal vein



Fig 1 *Left* sided adrenal phlebography showing the tumour The adrenal gland is seen within the lower part and median to the tumour



Fig 2 Renal aorthography The tumour can be seen at the upper part of the kidney (marked by arrows)

and 17-ketosteroids with a modified Zimmermann method (27) The steroids produced on incubation of the adrenocortical adrenoma (phosphate buffer with added glucose ATP, and TPN) were separated by paper chromatography according to Neher (30), whereafter cortisol and aldosterone were determined by the double labelling technique (23)

Laboratory findings

Blood analyses revealed pronounced hypokalaemia, slight hypernatraemia and metabolic alkalosis, whereas other values were normal The ECG also showed signs of hypokalaemia, such as typically flat T waves and positive after potential Potassium depletion was further demonstrated by the determination of total exchangeable potassium, which was only 1620 mEq or 27 4 mEq per kg body weight, a value considerably lower than those published for normal women by Moore et al (29), Ljunggren et al (25), and Crane et al (15)

Muscle biopsy analysis (table II) showed that total water and extracellular water (chloride space) were both increased further more, there was a high content of sodium and chloride Excess sodium, i e sodium not accounted for in the chloride space was above normal, indicating an increased amount of intracellular sodium Muscle potassium was low (about 2/3 of the normal value) in relation both to fat free solids and to total phosphorus The increase in excess sodium amounted to about 60 % of the decrease of potassium

The results of the kidney function tests are presented in table III Endogenous creatinine clearance was normal while PAH clearance was slightly decreased Concentration ability was decreased, the maximal urinary osmolarity being 542 mOsm/l after 18 hours of thirst in combination with i m pitressin administration There was transient, slight proteinuria The spun sediment contained a few red and white blood cells Urinary culture was negative In spite of potassium depletion the urinary potassium excretion was as high as 46—110 mEq per 24 hours when the patient was kept on a normal hospital diet supplying about 60 mEq of potassium per day The urinary pH was about 7 0 and did not change appreciably after ammonium chloride

Urinary aldosterone excretion was markedly increased (table IV), while the excretion of 17 ketogenic steroids was in the higher normal range and 17 ketosteroids were slightly lower than normal In comparison

incubation procedure demonstrated that the adrenal tumour produced not only aldosterone but also cortisol Thus, as in a number of cases reported earlier (21, 22), the adenoma also in this case was of a mixed type functionally The cortisol production of the adenoma *in situ*, could, however, not have been raised above the amount normally produced by a healthy subject, since this would have caused atrophy and inhibition of the cortisol production by the contralateral adrenal, this was not the case although cortisol production temporarily was slightly low immediately after operation

The low total exchangeable potassium and low muscle potassium content proved that this patient had a considerable potassium depletion The tissue analyses also showed an increase in the extracellular fluid and a gain in intracellular sodium However this sodium gain was smaller than the loss of cell potassium

The low total exchangeable potassium with increased Na_e/K_e ratio has earlier been observed in Conn s syndrome (8 15) and muscle analyses have demonstrated an increased content of sodium and a decreased content of potassium (10 28 37)

Balance data in Conn s syndrome have shown a smaller than expected gain of intracellular sodium as compared to the amount potassium lost (18) A similar relationship has been observed in rats with potassium depletion and alkalosis produced by the ingestion of deoxycorticosterone while on a potassium-deficient diet (13) This has been ascribed to an entrance of both hydrogen and sodium ions into the cells in exchange for potassium resulting in an intracellular acidosis The findings in the present case concerning the intracellular electrolytes are, thus, in agreement with observations by earlier investigators The relationship between the intracellular sodium and potassium content is compatible with the existence of an intracellular acidosis

The increase of the chloride space (extracellular fluid) in the muscle tissue may be an effect of the increased aldosterone secretion or of the potassium depletion *per se* (6 19)

The pre operative localization of the adrenal adenoma made it possible to use an appropriate operative technique for the extirpation, and also allowed palpation of the contralateral adrenal The exposure was easier than with the retroperitoneal exposure earlier used for the extirpation of adrenals and adrenal adenomas

Summary

A typical case of primary aldosteronism (Conn s syndrome) is described For localization of the aldosterone producing adenoma percutaneous catheterization of the left adrenal vein with retrograde injection of contrast was used Adrenal vein blood was obtained via the catheter for analysis of its content of aldosterone and cortisol The calculated aldosterone secretion reached 2 246 μg/24 hours as compared to a secretion rate of 100 and 156 μg/24 hours in two normal individuals investigated by the same technique The analyses revealed that the tumour produced considerable quantities of cortisol in addition to aldosterone

As localization of aldosteronomas with common roentgenological methods has been possible only in exceptional cases, the method described here seems to be of diagnostic advantage However, the catheterization technique is technically rather delicate and requires experience and training Furthermore, up to now it has been possible to use this technique with success only for the catheterization of the left adrenal vein Thus, where left-sided adrenal vein catheterization was attempted, the adrenal region could be visualized in 35 out of 47 cases (mainly normal subjects) However, if only the last 20 catheterizations are taken into consideration, there were only 2 failures, one because of a blood-pressure fall and the other because of sclerotic changes in the vessels Attempts to catheterize the right adrenal vein have been successful only in exceptional cases Similar experiences have recently been briefly presented by Chappel et al (9) using a technique similar to ours

Good evidence that the tumour was hormone-producing was obtained by analysis of the adrenal vein blood The demonstration of a high hormone production is of some importance because small adrenocortical adenomas can often be found at autopsy in humans without earlier clinical signs of adrenal disease A pre-requisite for obtaining representative values is that blood be collected under conditions which cause as little stress as possible The catheterization was therefore performed under local anaesthesia in the thigh, but otherwise without anaesthetics and the blood was collected while flowing spontaneously, i e without suction The values for the production of aldosterone and cortisol obtained in this way are in good agreement with those obtained by other methods Thus, on the basis of adrenal vein analyses in the two normal subjects we could estimate the aldosterone production per 24 hours as 50 and 78 μg, respectively, per single adrenal, corresponding to 100 and 156 μg, respectively, per pair of adrenals These values correspond well with the range of 60—240 μg for aldosterone secretion rate per 24 hours as measured by isotope dilution techniques in healthy normal subjects (2, 14, 17, 31, 36) Also, the aldosterone production as measured directly, in the present case of primary aldosteronism, was of the same order of magnitude as the values obtained by isotope dilution techniques in other cases with Conn's syndrome, where secretion rates of 295—1690 μg per 24 hours have been reported (17, 24, 32) The production of cortisol as measured in the adrenal vein plasma in our normal controls amounted to 14 7 μg per minute, which would represent a total secretion of 42 4 mg per two adrenals over the 24 hours This figure is rather higher than the figures of 17—29 mg per 24 hours obtained by Peterson and Wyngaarden using an isotope dilution technique (34) The explanation for this difference might be that the secretion rate as determined by us is based on the analysis of blood obtained during daytime when cortisol production is highest (34 35) while the method employed by Peterson and Wyngaarden includes the total 24 hours

The results of the analyses of adrenal vein blood as well as the results of the

incubation procedure demonstrated that the adrenal tumour produced not only aldosterone but also cortisol. Thus, as in a number of cases reported earlier (21, 22), the adenoma also in this case was of a mixed type functionally. The cortisol production of the adenoma *in situ* could, however, not have been raised above the amount normally produced by a healthy subject, since this would have caused atrophy and inhibition of the cortisol production by the contralateral adrenal; this was not the case although cortisol production temporarily was slightly low immediately after operation.

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The increase of the chloride space (extracellular fluid) in the muscle tissue may be an effect of the increased aldosterone secretion or of the potassium depletion *per se* (6, 19).

The pre-operative localization of the adrenal adenoma made it possible to use an appropriate operative technique for the extirpation and also allowed palpation of the contralateral adrenal. The exposure was easier than with the retroperitoneal exposure earlier used for the extirpation of adrenals and adrenal adenomas.

Summary

A typical case of primary aldosteronism (Conn's syndrome) is described. For localization of the aldosterone producing adenoma, percutaneous catheterization of the left adrenal vein with retrograde injection of contrast was used. Adrenal vein blood was obtained via the catheter for analysis of its content of aldosterone and cortisol. The calculated aldosterone secretion reached 2 246 μg/24 hours as compared to a secretion rate of 100 and 156 μg/24 hours in two normal individuals investigated by the same technique. The analyses revealed that the tumour produced considerable quantities of cortisol in addition to aldosterone.

Potassium depletion was shown by low extracellular potassium and low potassium content of skeletal muscle Intracellular sodium in muscular tissue was considerably increased The muscle samples were obtained by needle biopsy, using a technique suitable for repeated studies

Following removal of the adenoma, all biochemical abnormalities disappeared promptly and on examination one year after the operation the patient was completely healthy

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Megaloblastic Anemia and Neurologic Disturbances Combined with Folic Acid Deficiency

Observations on an Epileptic Patient Treated with Anticonvulsants

By

H A HANSEN, P NORDQVIST and P SOURANDER

An epileptic patient taking a combination of three drugs (diphenylhydantoin, phenobarbitone and trimethadione) developed a megaloblastic anemia and neurologic disturbances The anemia was due to folic acid deficiency In the literature we have found no information on the simultaneous occurrence and causative connections of folic acid deficiency and neurologic disturbances In the present case certain pathological changes unrelated to epileptic convulsions were seen at autopsy in the nervous system They may serve as a basis for further discussion concerning the possible role played by folic acid deficiency in neurologic diseases

Case report

A man 60 years of age was afflicted with epilepsy since childhood He was examined in hospital in 1955 and with a very careful neurologic examination in 1958 At that time he did not show any of the neurological symptoms which were later observed Nor did he have any hematological disorder during either period of hospitalization —all blood counts were normal Extensive calcification of the dura mater was noticed in 1958 on X ray of the skull Until 1955 he was given only phenobarbital for his epilepsy 1955—1958 he received the combination phenobarbital + diphenylhydantoin + trimethadione In Dec 1961 he again was admitted to hospital this time for marked anemia and total loss of all forms of cutaneous sensibility in his legs below knees and partial loss of sensibility in the rest of the legs and hands Atrophy and weakness of the skeletal muscles were further noted particularly in the legs below the knees The lower limbs were ataxic and walking was impaired Romberg's test was positive and the deep reflexes from the legs were abolished Babinski's sign was negative EMG from Tibialis anterior showed on both sides no spontaneous activity and with an attempt to contract only 1—2 spikes were observed They were of great amplitude and long duration indicating injury to the peripheral motor neuron To a lesser degree the same was noted on EMG from interosseus dorsalis of the left hand EMG from the same muscle of the right hand was normal EEG showed

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TABLE I Laboratory examinations and therapeutic data Microbiological determinations of folic acid and vitamin B_{12} were made as described by Hansen & Nystrom (10) Formimino-glutamic acid (FIGLU) was estimated as described by Hansen & Weinfeld (11) The d xylose test was performed according to the method described by Kerstell (15) Xanthurenic acid was examined in urine after a dl tryptophan load according to a method described by Maske (18)

Date	Test	Result	Normal value	Given drug/day
1961				
20/12	Serum B_{12} (pg/ml)	230	>175	13/12–20/12
	Serum folic acid (ng/ml)	1 0	>3 1	Diphenylhydantoin 0 3 g
27/12	Whole blood folic acid (ng/ml)	9 8	>22	Phenylbarbitone 0 45 g
	Whole blood ascorbic acid (mg%)	*0 07*	*0 40–0 70 (Dec)*	Trimethadione 0 6 g
1962				
4/1	FIGLU (uM/hr)	42	<30	20/12–14/3
	Serum B_{12} (pg/ml)	350	–	Phenylbarbitone 0 45 g
25/1	Serum folic acid (ng/ml)	0 7	–	Trimethadione 0 6 g
	Whole blood folic acid (ng/ml)	4 7	–	29/12–12/1
				Ascorbic acid 0 5 g i v
1/2	*Folic acid clearance test*		(S faecalis)	
	Control sample (ng/ml)	0 5	<1 0	25/1–1/2
	3 min sample (ng/ml)	50	>75	PGA 0 1 mg i m
	15 min sample (ng/ml)	0 4	>20	2/2–6/2
	30 min sample (ng/ml)	0 2	>4 0	PGA 15 mg i m
2/2	FIGLU (uM/hr)	12	–	–
6/2	d Xylose absorption test (g/5 hr)	2 9	>5	–
	Diagnex blue test (mg)	>0 6	>0 6	–
9/2	*Folic acid absorption test*		(S faecalis)	10/2–14/3
	Control sample (ng/ml)	0 5	–	PGA 15 mg i m
	1 hour sample (ng/ml)	15	–	–
	2 hours sample (ng/ml)	22	Peak value >50	–
	4 hours sample (ng/ml)	13	–	–
12/2	Whole blood ascorbic acid (mg%)	0 42	0 40–0 70 (Feb)	–
	Fat excretion (g/3 days)	11 4	<18	–
	Schilling s test (%)	14	>10	15/2–25/2
18/2	Xanthurenic acid in urine after 10 g tryptophan load (mg/24 hrs)	4 3	<30	Fe ^{3} 0 1 g i m

nothing abnormal An audiogram revealed no injury to the acoustic nerve Examination of the bone marrow showed the anemia to be of the megaloblastic type, and further examinations proved it to be due to folic acid deficiency By questions it was found that his diet had been low in folic acid and ascorbic acid but normal in vitamin B_{12} There were definitely no indications of chronic alcoholism No clinical signs of thiamin deficiency or of nicotinic acid deficiency were found There was no gingival hyperplasia Repeated Was

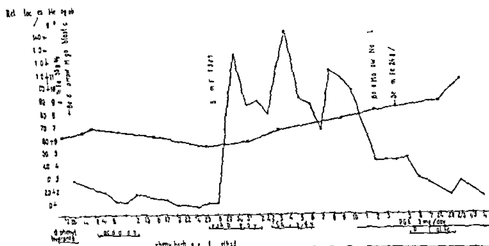


Fig 1 Hematological response to treatment

sermann tests on the blood were negative Four months after he entered the hospital the patient fell and broke several ribs and secondarily developed bronchopneumonia from which he died The laboratory findings confirming that the patient had folic acid deficiency are given in table I and the hematological response to treatment is recorded in fig 1 After withdrawal of diphenylhydantoin the patient was given food adequate in folic acid but no reticulocyte response was noted Since he showed deficiency of ascorbic acid he was given concomitant injections of this vitamin without effect on his anemia A clear response was, however noticed when treatment was changed to intramuscular injections of minute doses of folic acid

Comments on the hematological findings

Anticonvulsive drugs specially diphenylhydantoin but even barbiturates are known to induce megaloblastic anemia 3 9 12 It has been suggested that these drugs interfere with the utilization of folic acid 2 4 13) It is however hardly likely that the megaloblastic anemia in this case was due to any interference with folic acid by the anticonvulsive drugs administered There was no increase in circulating reticulocytes during the 35 days when diphenylhydantoin was withdrawn although the patient received enough folic acid with his food When parenteral folic acid was given the patient responded with a marked increase of reticulocytes in the blood — Yet the daily dose of folic acid given (only 0 1 mg) is of physiological magnitude and has no pharmacological action (11 17) Thus there could not be any interfering action of phenobarbitone and trimethadione on folic acid

The biochemical studies further indicate that the patient developed his megaloblastic anemia due to deficiency of folic acid The dietary data suggest some malnutrition Malnutrition as a *cause of* folic acid deficiency in epileptic patients has earlier been discussed by Flexner and Hartman (6) However, with the hospital diet the patient did not show



Fig 2 Extensive calcification of the falx and the dura mater covering the convexity of the cerebral hemispheres



Fig 3 Midsagittal section of vermis cerebelli Moderate shrinkage of folia of central lobule and culmen Slight atrophy of lingula Declive and inferior vermis appear grossly normal

the response normally found when megaloblastic anemia and folic acid deficiency are secondary to malnutrition (14) The folic-acid absorption test makes it further probable that the patient also had malabsorption of folic acid This decreased ability to absorb folic acid may well have been due to the anticonvulsive drugs the patient had received Lees (16) has shown that treatment with anticonvulsive drugs will produce a defect in absorption of vitamin B_{12} from the gut Concerning folic acid, Druskin et al (5) recently reported on a patient who had no hematologic improvement on a normal diet, but responded readily to a daily dose of 25 μg of synthetic folic acid taken orally though the anticonvulsant therapy continued throughout the hospital course Thus the defect in absorption of naturally occurring folic acid derivatives might be greater than could be predicted from the absorption test with pteroyl glutamic acid

Post-mortem examination

General pathological findings

Arthritic deformities were seen in several joints Both lungs showed congestion, massive edema and mucopurulent bronchitis Patches of bronchopneumonia were noted in the lower lobe of the right lung The heart was slightly enlarged due to dilatation of the right ventricle The coronary arteries revealed a moderate degree of arteriosclerosis There were heavy stasis and mild fatty degeneration of the liver The gall bladder appeared shrunken and contained numerous calculi No significant changes were seen in the spleen and lymph nodes Examination of the gastrointestinal tract revealed slight gastritis The other viscera were normal except for slight arteriosclerosis of the kidneys

Examination of the nervous system

The brain and spinal cord were fixed in 10 % formalin Blocks were removed from the frontal temporal, parietal and occipital lobes,

hippocampal format ons basal ganglia vari ous parts of the cerebellum lower bra n stem sp nal cord and nerve roots In add t on a p ece of a per pheral nerve was available for exam nat on Most of th s material was em bedded in paraff n and stained us ng the fol low ng methods hematoxyl n and eos n hematoxyl n and van G eson cresyl violet We l We gert Lillie and Luxol fast blue for myel n Palmgren s s lver technique for nerve cells and axons and Ranke s Victoria blue for astrocytes Scarlet red was used on frozen sect ons of the cord



F g 4 Low power v ew of central lobule demon strat ng uneven shrinkage of molecular layer preservat on of occas onal Purk nje cells th nning of granule layer and lamellar wh te matter Sl ght proliferat on of Bergman glia (Luxol fast blue stain)

Macros opic find ngs

After fixat on the bra n we ghed 1 240 g No d sease of the vessels at the base of the bra n was present There was extens ve calcificat on of the dura mater co ering the top of the cerebral hem spheres The falx was almost completely transformed in a nodular sh eld w th foci of bone format on (f g 2) There was con olut onal atrophy of moderately severe degree part cularly in the fronto-temporale reg ons The overly ng p a arach no d showed sl ght thicken ng and opac ty A sl ghter degree of atrophy was probably present throughout the remainder of the cere bral cortex In coronal sect ons through the hemispheres no focal les ons or abnormal t es were noted The ventricles appeared to be of ord nary s ze The r ependyma and choro d plexus appeared heal hy The basal gangl a mesencephalon lower bra n stem and sp nal cord d d not show any naked eye abnormal t es The cerebellum appeared to be of nor mal s ze When the verm s was d v ded sagit tally the con olut ons of the super or verm s appeared shrunken Th s shrinkage was con f ned to the central lobule and the anter or part of the culmen (f g 3 The sulci gaped w del n these atroph c reg ons Sl ght atrophy of the l ngula was present but all the o her parts of the verm s appeared normal In the cerebellar hemispheres there was sl ght a roph of the ans form lobules



F g 5 Low power v ew of transverse sect on of cerv cal cord Pallor of myelin is seen n columns of Goll The dorsal roots appear unaffected (We l We gert and Lill e stain)

M ro op find ng

Cerebrum A sl ght nerve-cell loss was seen in the frontal and temporal cortex There was also a m ld sub-p al fibr llary gl os s (marg n al gl os s of Chasl n) throughout the cerebral cortex No argyrophil c plaques or s gns of Alzhe mer s f brillary degenerat on were not ed The most remarkable cerebral change cons sted in a severe scleros s of the left Am mon s horn The gl al scarr ng d d not extend into the h ppocampal gyrus The right Am mon s horn appeared almost normal No s gn ficant abnormal t es were seen in other parts of the cerebrum

Cerebellum In the severely affected cortex of the super or verm s the molecular layer was reduced in width and showed a marked increase of the radially or ented f brils of the Bergman gl al cells The Purk nje cells were almost completely lost M ld reduct on of the granule layer was present (f g 4) The



Fig. 2. Extensive calcification of the falx and the dura mater covering the convexity of the cerebral hemispheres.

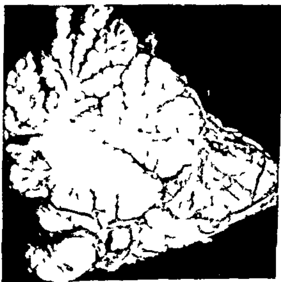


Fig. 3. Midsagittal section of vermis cerebelli. Moderate shrinkage of folia of central lobule and culmen. Slight atrophy of lingula. Declive and inferior vermis appear grossly normal.

the response normally found when megaloblastic anemia and folic acid deficiency are secondary to malnutrition (14). The folic-acid absorption test makes it further probable that the patient also had malabsorption of folic acid. This decreased ability to absorb folic acid may well have been due to the anticonvulsive drugs the patient had received. Lees (16) has shown that treatment with anticonvulsive drugs will produce a defect in absorption of vitamin B_{12} from the gut. Concerning folic acid, Druskin et al. (5) recently reported on a patient who had no hematologic improvement on a normal diet, but responded readily to a daily dose of 25 μg of synthetic folic acid taken orally, though the anticonvulsant therapy continued throughout the hospital course. Thus the defect in absorption of naturally occurring folic acid derivatives might be greater than could be predicted from the absorption test with pteroyl glutamic acid.

Post-mortem examination

General pathological findings

Arthritic deformities were seen in several joints. Both lungs showed congestion, massive edema and mucopurulent bronchitis. Patches of bronchopneumonia were noted in the lower lobe of the right lung. The heart was slightly enlarged due to dilatation of the right ventricle. The coronary arteries revealed a moderate degree of arteriosclerosis. There were heavy stasis and mild fatty degeneration of the liver. The gall bladder appeared shrunken and contained numerous calculi. No significant changes were seen in the spleen and lymph nodes. Examination of the gastrointestinal tract revealed slight gastritis. The other viscera were normal except for slight arteriosclerosis of the kidneys.

Examination of the nervous system

The brain and spinal cord were fixed in 10 % formalin. Blocks were removed from the frontal, temporal, parietal and occipital lobes,

TABLE II Effect of vitamin B deficiency on the human nervous system according to Pentschew (19) and Greenfield (8)

	Thiamine (B_1)	Nicotinic acid	Pantothenic acid	Pyridoxine (B_6)	B_{12}	Riboflavin	Folic acid
Peripheral neuropathy	+	+	+	+	+	—	?
Myelopathy	+	+	—	+	+	—	?
Encephalopathy	+	+	—	—	+	—	?

the cerebral hemispheres was not accompanied by calcification of other organs or clinical signs of hyperparathyroidism The cause of the calcification remains unexplained

It is generally known that sclerosis of Ammon s horn is a finding frequently observed at autopsy in the brain of chronic epileptics The Spielmeyer school of neuropathologists have provided clear evidence that the dense glial scarring of the Ammon s horn is due to vascular disturbances with or without anoxia (23) In the present case the sclerosis was strictly limited to the left Ammon s horn and regarded as secondary to the fits of grand mal type There was no clinical evidence of temporal lobe epilepsy and no focal lesion of the temporal lobes outside the left Ammon s horn

The atrophy of the cerebellar vermis was of a peculiar type being most severe in a restricted part viz the anterior region of the superior vermis Victor et al (24) described a restricted form of cerebellar cortical degeneration occurring in alcoholic patients with signs of malnutrition The pathological changes were entirely or mainly confined to that portion of the cerebellum which lies anterior to the primary fissure, i e the anterior lobe of Larsell This part of the cerebellum corresponds to the 'leg area' in the experimental animal and a lesion therein may be the cause of ataxia in the lower limbs In the present case a moderate degree of cortical atrophy was also seen in the cerebellar hemispheres especially in the ansiform lobules There was no story of alcoholism or general malnutrition in the present case

Pallor of myelin staining, most marked in the columns of Goll, has been repeatedly reported to occur in old age (7) This change was also seen in five of the eleven autopsy cases described by Victor et al (i e in all cases in which the spinal cord was examined) The degeneration in the dorsal columns seen in the present case might be primary but it seems more likely that it is secondary to the obliterative vascular changes and fibrosis of the distal nerve roots in the lumbo-sacral root pouches

The pathology of the spinal nerve root pouches has been much neglected It was studied by French neurologists at the beginning of this century In Sweden the study of this region was revived by Rexed et al (20, 21 22) However, in



Fig 6 Nerve roots proximal to spinal ganglion Concentric fibrous thickening and occlusion by hyaline mass of small arterial vessels (Hematoxylin and eosin stain)

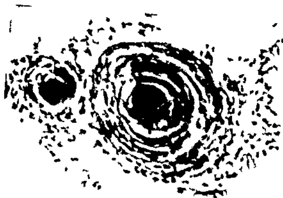


Fig 7 Fibrous laminar thickening of walls and occlusion by hyaline plugs of two small arteries in a dura pocket of lumbar region (Hematoxylin and eosin stain)

crowns of the convolutions were more affected than the depths A sligther degree of cortical atrophy involving mainly the Purkinje cells was seen in the cerebellar hemispheres especially in the ansiform lobules Fibrous gliosis was present in the lamellar white matter of the superior vermis but not in the central parts of the cerebellum The dentate nucleus was not seriously damaged

Medulla oblongata Moderate atrophy of nerve cells and considerable fibrous gliosis were present in the inferior olivary nuclei

Spinal ord In the lumbar cord there was a slight but definite pallor of myelin staining diffusely spread in the columns of Burdach and Goll In the thoracic and particularly in the cervical segments this pallor of staining was more pronounced and restricted to the columns of Goll (fig 5) A severe loss of myelinated fibres in this region was seen. The spinocerebellar tracts as well as Clarke s columns were intact The motor cells of the ventral horns were generally well preserved The juxta and intra medullary blood vessels in places showed slight thickening of their walls but were all patent No inflammatory changes were seen

Spinal nerve roots The proximal parts of the roots did not reveal any remarkable changes. The distal parts of several serially sectioned roots from the lumbar and sacral regions showed marked intra and extra neural fibrosis The walls of the dura root pouches showed considerable fibrous thickening Inflammatory infiltration was noticeably absent Marked changes were seen in small arteries and arterioles located between the dorsal and ventral root and inside the nerve fascicles (figs 6 and 7) The vascular changes were limited to the lower segments of the cord and consisted in a fibrous thickening and concentric lamellation of the entire wall of small arteries and advanced hyalinization of arterioles. The lumen of the affected arteries was strongly reduced by subendothelial collagenous deposits and in many instances occluded by a hyaline mass Evidence of organized thrombosis with recanalization was present in a small artery No signs of acute inflammatory changes were observed in the vessels

Spinal ganglions were not available for study

Peroneal nerve Stained sections and with polarization microscopy unstained ones did not reveal any significant changes

Autopsy comments

Atlas et al (1) reported calcification of the dura mater together with nephrocalcinosis and metastatic calcification of various organs in a case of masked hyperparathyroidism In the present case extensive calcification of the dura covering

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previous publications almost nothing is mentioned about vascular changes in the root pouches The concentric sclerosis of small arteries and arterioles observed in our case was restricted to the lumbo sacral roots There were no signs of atherosclerosis in sensu strictiori in the spinal or root vessels, and no evidence of a specific inflammatory process The patient had not been subjected to X-ray examination of the dural sack The examination of other organs did not reveal any signs of diffuse collagen disease The etiology of the vascular changes thus remains obscure

It is a well established fact that most of the B vitamins are implicated in the metabolism of the nervous system Deficiency of individual B vitamins may lead to histologically well regognized changes in the nervous system and neurologic disturbances (table II) Riboflavin deficiency in experimental animals may result in degenerative changes of peripheral nerves and spinal cord However, experiments in human volunteers have not resulted in any lesions of the peripheral and central nervous system (8) So far nothing is known about the effect of folic acid deficiency on the nervous system Although folic acid is useful in some macrocytic anemias it differs from vitamin B_{12} in being unable to prevent involvement of the central nervous system in pernicious anemia In the present case there was no B_{12} deficiency and the changes of the spinal cord were not like those of subacute combined degeneration There was no clinical evidence of deficiency of B vitamins other than folic acid Although the pathogenetic mechanism remains unsolved the possibility must be considered that the lesions in the cerebellum, spinal cord and root pouches might be connected with the severe folic acid deficiency of the patient

Summary

A clinical, hematological and neuropathological study was made on a case of chronic epilepsy The patient had received anticonvulsive therapy for about fifty years when he developed a megaloblastic anemia This was due to folic acid deficiency No interference with folic acid metabolism by the anticonvulsive drugs was found in this case

Neurologic symptoms not related to the epilepsy occurred simultaneously with the megaloblastic anemia They were probably a consequence of degenerative changes found in the cerebellum, spinal cord and spinal root pouches The possibility that these changes were caused by folic acid deficiency is discussed

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Serratia Marcescens Septicemia

A Case Report

By

PENTTI REISSELL and ELLI JANSSON

Serratia marcescens also called Chromobacterium prodigiosum is often found in water and soil This short Gram negative rod grows in red pigmented colonies It may also contaminate food The Italian pharmacist Bizio declared in 1823 that it was the cause of an outbreak of red colored polenta or bleeding mush' He named it Serratia marcescens

Serratia marcescens is potentially pathogenic to man The first case of the disease in man was described by Wordward and Clarke in 1913 (19) The patient suffered from chronic cough and the sputum was colored red by Serratia Other cases of pseudohemoptysis caused by Serratia have been reported since (5 15) It has been found to cause pneumonia (3) pleural empyema (12) meningitis (1 14) wound infections (6 7) urinary tract infections (6 10 16 18) and intestinal infections (11) Serratia has also caused cross infections especially in infant (11 14) and urologic wards (10 16 18)

Submitted for publication February 5 1964

Severe, usually fatal cases of sepsis may also be produced by Serratia marcescens, especially in patients who have a debilitating disease or have received long term antibiotic or steroid therapy We have come across in the literature 7 reports of such cases of Serratia marcescens septicemia with fatal outcome (7, 8, 9, 13, 14 17 18) In reporting on the present case, the eighth, we wish to draw attention to the pathogenicity of Serratia marcescens, which is often regarded as a saprophyte

Case report

Clinical findings

The patient, a woman of 41 was admitted in Sept 1962 to the Aurora Hospital in a stuporous septic condition She had been addicted to narcotics and analgesics for 10 years For intravenous injections she had dissolved narcotics in highly impure vehicles, e g mains water On admission she was agonic had septic fever and muscle twitchings In the skin numerous injection scars were noted some of them infected Pulse 96/min regular

The autopsy diagnoses were Endocarditis ulcerosa valvulae aortae (et mitralis) Pyelonephritis chr c abscesibus renis sin Tuberculoma lobi sup pulm dx

Microbiological findings

The strain isolated from the patient grew on the blood agar plate at 37° C after 18 hours incubation in convex shiny colonies 0 5—1 5 mm in diameter, which were first orange colored but changed rapidly to an intense red The colonies produced a marked β hemolysis on the blood agar plate On incubation at 25 C the strain first grew in colorless then blood red colonies 0 1—0 5 mm in diameter In broth a red sediment formed on the bottom after 18 hours at 37 C

Microscopic examination showed that the strain was a short, motile Gram negative rod The biochemical reactions were as follows the strain fermented glucose saccharose and mannitol forming acid but no gas It did not ferment lactose Indole— H_2S — urea —, citrate + gelatin +

Antibiotic sensitivity tests by Ericsson s disk method (4) showed that the strain was completely resistant to penicillin erythromycin oleandomycin novobiocin, bacitracin methicillin doctacillin colimycin and polymyxin and moderately resistant to tetracycline It was sensitive to sulphonamides streptomycin chloramphenicol neomycin and kanamycin

The pathogenicity for mice of the isolated strain was studied by injecting 18-hour broth culture intraperitoneally 0 2 ml of the culture killed 2 out of 3 mice in 24 hours

The patient s serum agglutinated both O antigen and H antigen prepared from the isolated strain in a titer of 1 160

Comments

Of special interest is the resistance to many antibiotics of the Serratia marcescens strain isolated It accords with the observations made by other investigators Usually, the strains studied have been sensitive only to neomycin and kanamycin (3, 6, 8, 10, 13, 16), sometimes also to streptomycin and chloramphenicol (9, 12) It is thus understandable that the therapeutic possibilities for Serratia marcescens septicema are very limited

In the reported case there was advanced chronic pyelonephritis and papillary necrosis Bengtsson has established that patients with papillary necrosis use twice as much analgesics, particularly phenacetin, as other chronic pyelonephritis patients (2) The abuse of analgesics has an obvious role in the pathogenesis of chronic pyelonephritis and papillary necrosis in these patients In the present case the part played by Serratia marcescens was clearly due to the sharp decrease in resistance The septic condition probably originated via the renal route although the possibility of intravenously produced infection cannot be ruled out

Summary

A fatal case of Serratia marcescens septicemia in a middle aged drug addict is reported The patient s serum had antibodies in a titre of 1 160 against O- and H antigens prepared from the strain isolated from her blood, urine and autopsy samples

The resistance of Serratia marcescens to several antibiotics limits the therapeutic chances considerably Serratia infections must therefore be taken very seriously, especially the prevention of cross infections



Fig 1 Aortic valve revealing typical inflammatory changes due to bacterial endocarditis S marcescens bacteriae are not seen with this magnification

TABLE I Results of laboratory tests

Blood	
Hemoglobin	6 1 g%
Erythrocytes	2 2 mill
Leucocytes	37 700
(Differential count shift to left)	
Thrombocytes	88 000
Creatinine	5 6 mg%
Sodium	151 mEq/l
Potassium	5 1 mEq/l
Calcium	7 2 mg%
Proteins	5 6 g%
pH	7 38
Thymol turb	0 36 (ext)
Alk phosphatase	5 1 B L units
GOT	26
Prothrombin index	69
Urine	
Protein — Glucose —, Specific weight 1 020	
Sediment numerous leucocytes	
Bacteria Serratia marcescens	
ECG	
Signs of left atrial enlargement and left ventricular hypertrophy with left diastolic overloading	

and collapsing BP 110/40 Rough systolic and high pitched diastolic murmurs were heard in the aortic area The liver was enlarged The results of the laboratory tests are shown in table I Serratia marcescens was isolated from blood and urine samples

The patient was treated with digitalis large doses of penicillin and streptomycin and for the last two days with tetracycline intramuscularly She was given blood transfusions with packed red cells and infusions of fluids but died after 5 days in hospital

Autopsy

The aortic valve displayed pronounced endocarditic changes in one cusp thickening deformation of the valve and ulceration The endocarditic change was of lesser extent in the mitral valve Microscopic examination revealed changes of acute bacterial endocarditis (fig 1) Abscess resembling inflammatory foci were seen to extend from the aortic valve as far as the cardiac muscle A caseous necrotic focus was seen in the upper lobe of the right lung the lower lobes displayed definite hemorrhagic and edematous change The spleen was enlarged and infiltrated by small infarction necroses The liver was hyperemic There was profuse scar formation on the surface of the kidneys Partial destruction of normal structure was observed in the parenchyma and the right kidney displayed several cavities containing pus The pelvis was enlarged and the mucosa inflamed Pus was encountered in the calyces and some of them were ulcerated The changes in the left kidney were identical except for the abscess formation The renal changes suggested chronic pyelonephritis and papillary necrosis

Biopsy and pus samples taken at autopsy from the cardiac valve and kidneys gave growth of Serratia marcescens TB culture from the necrotic pulmonary focus was positive

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Summary

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The resistance of Serratia marcescens to several antibiotics limits the therapeutic chances considerably Serratia in*fect ons* must therefore be taken very seriously, especially the prevention of cross infections

Acknowledgement

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Turnover Rate of Paraproteins in Myelomatosis

Studies on the Turnover Rate of Serum Paraproteins after Labelling in Vivo, with Special Reference to Repeated Turnover rate Determinations

By

AAGE DRIVSHOLM[1]

Application of isotopes to the study of protein turnover in myelomatosis was first made by Hardy and Putnam in 1953 (10) Since then many studies have been performed with *in vivo* as well as *in vitro* labelling of the proteins (cf int al 4 9 11 22)

The object of the present study was 1) To elucidate the turnover rate of serum paraproteins in a large series of patients with myelomatosis 2) to ascertain whether the turnover rate of the paraproteins changes during the course of the disease and 3) to find out whether Melphalan (1 phenylalanine mustard a cytotoxic agent used in the treatment of myelomatosis (1 21 28)) affects the turnover rate of the paraproteins

Material and methods

The study comprises 22 patients suffering from myelomatosis 7 of whom were included in a previous study (5) The diagnosis of myelomatosis was based on the bone marrow findings and was later confirmed by the demonstration of an abnormal serum protein component by Tiselius electrophoresis and a paraprotein component by immuno-electrophoresis All the patients were admitted during the period 1958—1962 to Medical Department A Rigshospitalet Copenhagen The present study comprises a group of the patients from whom a serum myeloma protein (M protein) could be isolated by a single precipitation with ammonium sulphate (5)

Five of the 22 patients had been treated prior to the first turnover rate study (table I) Prednisone and urethane had not been administered during the 6 months preceding the study except in case 35 whose urethane medication had *not* been discontinued until 2 months before the turnover rate determination

As a general rule the patients were ambulatory during the experimental period

Labelling of the M proteins was performed *in vivo* by glycine 1 C-14 (Amersham England) The glycine 125—200 μC, was given

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TABLE I Half life of serum paraprotein in 22 patients No refers to the case numbers used in other publications on the same series (an exception is a previous paper on the turnover rate of myeloma proteins (5) in which cases 4 9 38 39 62 73 and 100 are listed as cases 14938 14637 15C01 10096 12714 8087 and 14213) Myeloma cells are taken to include plasma cells and plasmocytic reticulum cells The haemoglobin values are from the 1st experimental day and do not in any case differ essentially from the values found at a later stage of the experimental period The type and quantity of the M components were determined by Tiselius electrophoresis and abnormal protein in the urine by paper electrophoresis after concentrating the urine The $(NH_4)_2SO_4$ solutions used in the salting out of paraproteins are stated in vol % of a 3 5 molar stock solution The salted-out proteins were studied by paper electrophoresis (homogeneity of M protein) and immuno-electrophoresis Pure indicates pure paraprotein the components in brackets in the same column are the contaminations found together with the paraprotein component. Erysan = 2 3 -dichloroethylene β naphtylamine

No	Sex	Myeloma cells (%)	Hgb (g%)	Type: Paraprotein	Type: M component	Concentration (g %): Total serum prot	Concentration (g %): M component	Abn urine protein	Treatment before study	Vol % $(NH_4)_2SO_4$	Homogeneity of M prot (%)	Imm electr studies	$T^1/_2$ (days)
2	♂	15 9	7 4	γss	γ	13 5	10 5	β	0	48	94	Pure	15 2
4	♀	94 7	8 7	γss	γ	9 5	5 9		0	39	92	(α_2 lipo)	9 1
6	♂	34 9	9 3	γss	γ	7 8	3 6	γ	0	46	96	(alb & α_2 lipo)	12 0
7	♀	16 7	11 5	γss	γ	8 8	3 4	0	0	46	95	(γss)	10 9
9	♂	16 0	9 2	γss	γ	9 5	3 6		0	43	91	Pure	12 1
37	♀	42 4	10 6	γ1 A	β	8 0	4 3	β	0	46	91	(γss)	6 9
33	o	75 5	7 4	γss	γ	16 1	13 7	β	0	46	96	Pure	14 0
34	♀	32 7	10 0	γss	γ	8 3	4 7	β	0	50	94	(γss)	12 6
35		22 7	11 2	γss	γ	9 2	4 2	)	Urethane	42	98	Pure	12 5
38	o	35 7	6 9	1 A	β	10 9	8 1	β	0	41	97	(γss)	4 5
39	o	15 9	7 5	γss	γ	11 6	6 8	γ	Urethane Prednisone	45	94	(trans & hapto)	13 3
49	♂	65 6	10 1	γss	γ	11 7	8 0	γ	0	40	97	(γss)	9 8
56	o	30 7	10 8	γss	γ	9 4	4 4		0	36	79	(alb)	11 3
60	*	33 3	8 8	ss	γ	9 3	4 3	γ	0	48	91	Pure	12 7
61	‹	35 9	10 4	μ	β	8 5	5 3	β	0	46	83	(γss & hapto)	5 6
62	›	24 9	8 4	ss	γ	10 2	5 4		Urethane Prednisone	39	97	(γss)	7 5
65		8 5	6 9	γss	γ	12 0	8 2	γ	0	38	97	Pure	11 6
70	♂	33 0	6 2	γss	γ	10 2	6 8	β	0	42	92	(γss)	9 2
71		33 ?	6 3	γss	γ	12 5	9 4	β	0	37	97	Pure	15 4
73	›	59 0	11 1	ss		11 0	7 0	β	Urethane Prednisone	43	95	Pure	15 6
97		14 3	9 0	1 A	β	9 0	5 0	β	0	38	89	Pure	7 9
100	›	10 3	8 9	ss	γ	6 9	1 4	β	Erysan	39	84	(γss)	9 7

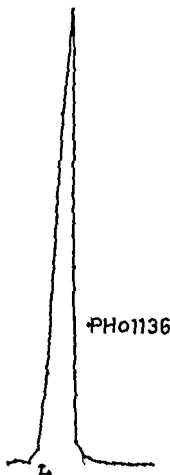


Fig 1 Case 73 Paper electrophoresis on a salted out γSS paraprotein

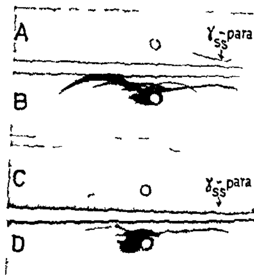


Fig 2 Immuno-electrophoresis on a salted-out γSS paraprotein (same as in fig 1) A Developed with a horse anti serum against normal pooled human serum C Developed with a corresponding goat anti serum In both instances normal serum was run as a control (B and D)

as a single intravenous injection in 12 5—20 ml isotonic NaCl solution The specific activity of the various batches ranged from 3 5 to 4 8 mC/mM

Blood samples for determination of the activity were drawn at 8 a m daily for 2—3 weeks after the administration of glycine The serum samples were stored at —20° C until all samples for the patient concerned could be studied together

Twice weekly the haemoglobin level total serum protein, creatinine, and urea were determined

24-hour urines were collected in patients with proteinuria The amount of protein was determined by the method of Tidstrom (25) and the excretion of protein calculated in 3 day periods owing to the slight variations in the 24-hour excretions (26)

Isolation of the M protein in serum was done by salting out, using ammonium sulphate The procedure for *determination of salting-out maximum for preparation of the salted-out myeloma protein for activity measurement and for counting of radioactivity* have been described in a previous paper (5)

Protein homogeneity and identity The salted out M proteins were studied by paper electrophoresis (26) as well as by immuno-electrophoresis (3) One sample was studied in each turnover rate determination As the antibody in the immuno-electrophoretic study we used horse and goat antiserum against normal, pooled human serum (6) If immuno electrophoresis revealed traces of more than 2 protein components contaminating the paraprotein, the patient was excluded from the study Figs 1 and 2 show the paper and immuno-electrophoretic findings in a salted out paraprotein

Calculation of the turnover rate was performed by plotting the logarithm of the specific activity of the M protein in the individual samples against time (fig 3) In this semilogarithmic system the radioactivity decreases linearly from the 3rd day after the administration of

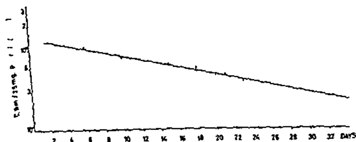


Fig 5 Case 60 Half life (T 1/2) of a γss paraprotein. In this case the activity measurements were continued for up to 33 days after the administration of glycine 1 C-14 The fall in specific activity follows the same straight line throughout the period

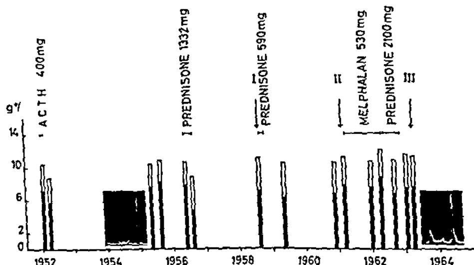


Fig 6 Case 73 Protein changes in a patient with myelomatosis followed for 12 years The black parts of the columns represent M protein the total height total protein The arrows indicate the time of the three turnover rate determinations (table II and fig 7) Nature and duration of treatment stated above the columns. The results of Tiselius electrophoresis in 1955 and 1963 are inserted in the figure

T 1 2 of γ_{ss} paraprotein (18 patients) ranged from 6 9 to 15 6 days (mean 11 9 2 3 S D)

The relation between type of paraprotein and T 1 2 is illustrated in fig 4 As is apparent from the figure the T 1/2 values in the γ_A group are significantly lower than those in the γ_{ss} group ($P < 0.001$) It is notable also that the half life of the γ_μ paraprotein studied is shorter than that of all studied paraproteins in the γ_{ss} group

No correlation was found between the T 1/2 values and total protein or M pro-

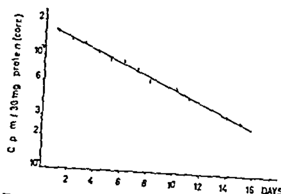


Fig 3 Case 61 Half life (T 1/2) of a $\gamma\mu$ para protein The logarithm of the specific activity (in counts/min) is plotted against time (in days) T 1/2 = 5 6 days

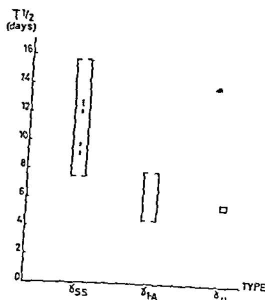


Fig 4 Half lives (T 1/2) in relation to types of paraprotein The difference in T 1/2 in the γSS group (mean 11 9 days) and the γ1—A group (mean 6 4 days) is significant (P 0 001)

glycine Calculation of the half life was done according to the formula $T\,1/2 = \frac{\ln 2}{a}$ in which a is the regression coefficient of the line (29)

Control of steady state A constant total body weight during the experimental period in a patient with unchanged total protein in the serum (and a constant proteinuria if present) was taken to indicate a steady state with respect to protein turnover The patient s body weight was checked weekly during the experimental period

An exponential fall in specific activity was assumed to indicate that an approximate equilibrium between the intravascular and the extravascular paraprotein pools had been present To ascertain whether this equilibrium is present as early as the 2nd—3rd experimental day or whether the slope alters beyond the experimental period (2—3 weeks the activity measurements were continued in one case for up to 33 days after the administration of glycine (case 60)

The influence of prednisone upon the concentration of total protein and M protein in the serum was studied by following these values for a number of years during intermittent prednisone therapy in 2 cases (Nos 39 and 73) who had previously responded to prednisone (cf 27 cases 10096 and 8067)

The influence of prednisone upon the turnover rate curve was investigated in one case (No 73) by administering 60 mg prednisone daily from the 8th to the 15th day of the first turn over rate determination

Repeated turnover rate determinations were done in 5 cases in order to detect possible changes in T 1/2 during the course of the disease Four of these patients had been treated with Melphalan prior to the last turnover rate determination

Results

Table I lists the half life values of the serum paraprotein in 22 patients as well as other relevant laboratory results Five patients were excluded from the study because the salted out M proteins did not fulfill the demands for homogeneity

T 1 2 of $\gamma\mu$ paraprotein (Bence Jones protein in *serum*) was investigated in one case (No 61) and found to be 5 6 days Fig 3 depicts the turnover rate curve

T 1 2 of γ1—A (β_{2}—A) paraprotein (3 patients) ranged from 4 5 to 7 9 days (mean 6 4 ± 1 75 S D)

other findings (table II) The protein findings in the other patient who was given intermittent prednisone therapy (No 39) varied analogously to the case illustrated in fig 6

Prednisone and turnover rate This aspect was studied in one of the patients (No 73) in whom prednisone caused a reversible reduction in the concentration of M protein in the serum As is apparent from fig 7 (curve I), 60 mg prednisone daily did not alter the slope within the observation period

Repeated studies of turnover rate In 4 cases a turnover rate determination was carried out twice at an interval of 11—29 months in one patient *3 times* at intervals of 30 and 25 *months* The results are recorded in table II which shows that the half life in 3 patients (Nos 39, 73 and 7) changed insignificantly (P ~ 0 1) from one determination to the other

Two patients (Nos 70 and 71) showed a significant reduction in the turnover rate between the 2 determinations (P < 0 02) In both cases the amount of abnormal M protein in the serum decreased and simultaneously the haemoglobin level increased (table II) This applies particularly to case 71 in whom Melphalan was clinically very active Fig 7 shows the 3 turnover rate determinations in case 73 fig 8 the two turnover rate determinations in case 71

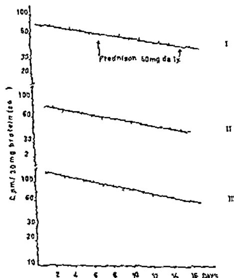


Fig 7 *Case 73* Result of 3 turnover rate determinations on a γSS paraprotein The interval between the 1st and 2nd *determinations* was 30 months, between the 2nd and 3rd 25 months. The three T 1/2 values were found to be 15 6 15 4 and 15 7 days From the 7th to the 15th day of the first *determination* (I) the patient received 60 mg *prednisone* daily (*without* any effect upon the slope of the curve)

Discussion

The problems attending the use of isotopes for studying the plasma protein turnover rate have been summarized by McFarlane (1) In the case of *in vivo* labelling the main sources of error are

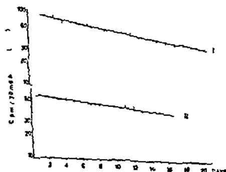


Fig 8 Case 71 Half life of a γSS paraprotein before (I) and after (II) Melphalan therapy Between the two determinations the patient received 13 series of Melphalan (total 530 mg) over 19 months T 1/2 15 1 (I) and 19 6 days (II)

TABLE II Result of repeated turnover rate determinations in 5 patients with typ γSS myelomatosis. Symbols as in table I In cases 70 and 71 a significant change occurred in the T½ (P < 0 02) The other individual changes are insignificant (P > 0 1)

No	Study	Interval between studies (months)	ESR (mm/1 hr)	Hgb (g%)	Concentration (g%) Total serum prot	M component	Homogeneity of M prot (%)	Imm -electr studies	Treatment between studies	T ½ (days)
39	I	—	143	7 5	10 7	6 3	94	(transf & hapto)	—	13 3
	II	29	154	8 7	9 5	5 6	95	(transf & α₂ lipo)	Prednisone Urethane 117 g	12 7
73	I	—	106	11 1	11 0	7 0	95	Pure	—	15 6
	II	30	108	10 4	11 5	7 6	96	Pure	Prednisone	15 4
	III	25	102	9 0	11 3	7 5	99	Pure	Prednisone & Melphalan 530 mg	15 7
7	I	—	70	11 5	8 8	3 4	95	(γSS)	—	10 9
	II	19	20	12 1	9 2	2 5	92	(γSS)	Melphalan 260 mg	11 1
70	I	—	150	6 2	10 2	6 8	92	(γSS)	—	9 2
	II	11	84	8 0	10 0	5 2	95	Pure	Melphalan 1560 mg	13 9
71	I	—	158	6 3	12 5	9 4	97	Pure	—	15 4
	II	19	55	11 3	9 3	4 3	96	Pure	Melphalan 530 mg	19 6

tein in the serum The studies also failed to show any correlation between the haemoglobin level and T 1/2 (table I)

Control of steady state Two patients could not be weighed during the experimental period because of painful vertebral fractures (Nos 56 and 62) Two patients on diuretic therapy, but without visible oedema (Nos 32 and 34) showed weight loss (< 4 kg) during the turnover-rate study The remaining patients were in a steady state with respect to the above mentioned criteria

In all cases the activity decreased linearly from the 3rd experimental day without changes in the slope Fig 5 shows that the activity is still decreasing along the same slope, 33 days after the administration of glycine

Changes in serum proteins during the course of the disease are illustrated, for one of the 2 studied cases, in fig 6 (case 73) In this case prednisone could temporarily reduce the concentration of M protein (and total protein) in the serum During the periods off prednisone treatment the protein values were fairly constant, although the concentrations of M protein and total protein showed a tendency to a slow increase during the course of the disease In this case Melphalan had no definite effect upon the serum proteins or

other findings (table II) The protein findings in the other patient who was given intermittent prednisone therapy (No 39) varied analogously to the case illustrated in fig 6

Prednisone and turnover rate This aspect was studied in one of the patients (No 73) in whom prednisone caused a reversible reduction in the concentration of M protein in the serum As is apparent from fig 7 (curve I), 60 mg prednisone daily did not alter the slope within the observation period

Repeated studies of turnover rate In 4 cases a turnover rate determination was carried out *twice* at an interval of 11—29 months in one patient *3 times* at intervals of 30 and 25 months The results are recorded in table II which shows that the half life in 3 patients (Nos 39 73, and 7) changed insignificantly ($P < 0.1$) from one determination to the other

Two patients (Nos 70 and 71) showed a significant reduction in the turnover rate between the 2 determinations ($P < 0.02$) In both cases the amount of abnormal M protein in the serum decreased, and simultaneously the haemoglobin level increased (table II) This applies particularly to case 71 in whom Melphalan was clinically very active Fig 7 shows the 3 turnover rate determinations in case 73 fig 8 the two turnover rate determinations in case 71

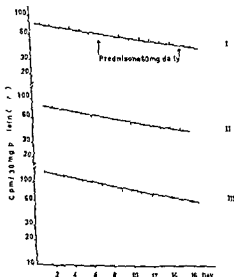


Fig 7 Case 73 Result of 3 turnover rate determinations on a γSS paraprotein The interval between the 1st and 2nd determinations was 30 months between the 2nd and 3rd 25 months The three T 1/2 values were found to be 15 6 15 3 and 15 7 days From the 7th to the 15th day of the first determination (I) the patient received 60 mg prednisone daily (*without* any effect upon the slope of the curve)

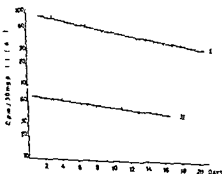


Fig 8 Case 71 Half life of a γSS paraprotein before (I) and after (II) Melphalan therapy Between the two determinations the patient received 13 series of Melphalan (total 530 mg) over 19 months T 1/2 14 1 (I) and 19 6 days (II)

Discussion

The problems attending the use of isotopes for studying the plasma protein turnover rate have been summarized by McFarlane (14) In the case of *in vitro* labelling the main sources of error are

protracted labelling of the proteins and re-utilization of labelled amino acid formed by protein degradation To reduce these errors, glycine was used in the present study (5) In the case of *in vitro* labelling the primary problem is whether the proteins are denatured after the iodination and whether they behave like the unlabelled proteins after re-injection

Irrespective of the labelling method, it is important to make sure that the proteins are pure The homogeneity of the salted-out fraction was checked, in the present study, by paper- as well as immuno-electrophoresis In those cases where the M proteins were found to be inhomogeneous in the immuno electrophoretic study, there was only a trace of contamination by at the most 2 minor protein fractions However, as immuno-electrophoresis of normal serum shows between 20 and 30 fractions (3) with many antisera (fig 2), some contamination might be expected

The variation in the half-life of the individual paraproteins has been pointed out in a previous paper (5) and was found also in this series (cf fig 4) Gabuzda (9) found a corresponding variation in his study of autologous I^{131}-labelled paraproteins The T 1/2 values in Gabuzda's material (7 patients) ranged from 5 2 to 12 2 days, the T 1/2 values in the present series from 4 5 to 15 6 days (22 patients) Considering the marked variation in the values it is not surprising that Putnam and Hardy (19) and Osserman et al (17) could find T 1/2 values of 20 and 21 days in single experiments on *in vivo* labelled M proteins

Turnover rate and types of paraprotein In the present study γ_{1-A} paraproteins differed from γ_{SS} paraproteins in having a shorter half-life This difference does not appear to have been observed previously, perhaps because previous series have been too small to permit comparisons A short half life means a rapid protein turnover Since myeloma cells form M protein (15) and perhaps also play a role in their breakdown (16), the myeloma cells must be expected to be, in general, more active in myelomatosis of the γ_{1-A} than the γ_{SS} type An increased cellular activity and a short half life of paraprotein may promote the cellular changes (irregular cell outline, PAS positive nuclear inclusions, naked, structureless nuclei, and amyloid like masses of cytoplasm in the smears) seen in γ_{1-A} myelomatosis (6, 7)

Turnover rate and treatment Four of the 22 patients had been treated, prior to the study, with urethane or urethane + prednisone and one with Erysan (2,3 dichlor ethylene-β naphtylamine) (cf table I) The mean T 1/2 in the 5 treated patients was 11 7 days and in the 13 untreated patients of the γ_{SS} group 12 0 days Thus, the treatment does *not* seem to have influenced the turnover rate

Prednisone had no immediate influence upon the half-life of the paraproteins, in a single determination (fig 7) This also applies to 6 6 S γ globulin (22) The serum level of M protein is in some cases influenced by prednisone (27) and ACTH (8), but the changes seem to be reversible (fig 6)

The effect of urethane upon the turnover rate of the paraproteins is unknown In one case the T 1/2 of normal γ globulin appears to have been reduced by urethane therapy during the turnover rate

determination (12) Reversible changes in the serum level of M protein have been described during urethane therapy (20) and were observed also in one of our cases (No 39)

The influence of Erysan upon the protein turnover in myelomatosis is unknown

By administering urethane and prednisone intermittently and by withdrawing the medication 3—6 months before the turnover rate determination, it was assumed that any influence by urethane or prednisone upon the repeated half-life determinations in cases 39 and 73 (table II) had been ruled out The repeated turnover rate determinations thus showed that the half life of γ_{SS} paraprotein is unchanged during the course of the disease (maximum observation period 55 months) This agrees with the findings of Lippincott et al (13) (2 T 1/2 determinations on an M protein at an interval of 3 months)

Corresponding studies on γ_{1-A} paraprotein could not be performed Case 32 went into remission after 300 mg Melphalan and has not had any M fraction for 20 months (as compared with 4 3 g/100 ml M protein prior to the treatment) The other two patients with γ_{1-A} paraproteinaemia (cases 38 and 97) died shortly after the first turnover rate determination

Effect of Melphalan on the turnover rate Two of the 4 patients whose turnover rate was determined before and after Melphalan therapy showed a significant alteration in T 1/2 (cases 70 and 71 cf table II) In these two patients Melphalan also had a definite clinical effect as evaluated by the subjective complaints and laboratory results (ESR, haemoglobin level, total protein and M protein in the serum number of myeloma cells in the bone marrow)

There is no definite explanation why the turnover rate was slower after Melphalan therapy in these two cases As already mentioned no correlation between the turnover rate and the content of protein in the serum (total protein or M protein) could be demonstrated The pool size of the paraprotein cannot be evaluated by the present method Since the intravascular pool makes up 56—85 per cent of the total pool of paraprotein (9), the recorded decrease in the concentration of M protein in the serum during Melphalan therapy (table II) must indicate a decrease in the total pool Considering that the turnover rate of paraprotein had become slower at the same time the total production of paraprotein must be reduced further than indicated by the serum level Whether this reduced production is caused by a reduction in the ability of the individual cell to produce paraprotein or by a reduction in the number of paraprotein producing cells still remains unelucidated This question cannot be solved merely by counting the number of myeloma cells in the bone marrow before and after Melphalan therapy as paraprotein is produced also in cells other than the myeloma cells of the bone marrow Thus paraprotein may be formed in the lymph nodes in Waldenström's macroglobulinaemia (23)

A reduced turnover rate despite a reduced protein pool is also observed in certain other conditions (cf the slow turnover rate of γ globulin in patients suffering from hypo- and agammaglobulin

aemia (2)) The nature of this 'protein-saving" mechanism is unknown

Turnover rate and course of the disease In a previous study on the turnover rate of M proteins (5) a correlation was found between the T 1/2 of M protein and the duration of the disease (the shorter the T 1/2, the poorer the prognosis) This finding presupposed that T 1/2 remained unchanged during the course of the disease, as proved in the present study The previous investigation (5) comprised only 5 patients The use of Melphalan in the treatment of myelomatosis has precluded further studies of the correlation between T 1/2 and prognosis

Summary

Turnover-rate determinations of serum paraproteins in 22 patients with myelomatosis are reported The paraproteins were labelled *in vivo* by intravenous injection of glycine-1-C-14 In 18 of the cases the paraproteinaemia was of the γ_{SS} type, in 3 of the γ_{1-A} (β_{2-A}) type, and in one of the γ_μ type (Bence-Jones protein in the serum)

T 1/2 in the γ_{SS} group was 11 9 $\pm$ 2 3 S D days (range 6 9—15 6 days), in the γ_{1-A} group 6 4 $\pm$ 1 75 S D days (range 4 5—7 9 days) The T 1/2 of a γ_μ paraprotein was determined as 5 6 days There was a significant difference between T 1/2 in the γ_{SS} and γ_{1-A} groups ($P < 0\ 001$)

In two patients the turnover rate was determined twice and in one patient 3 times at intervals of 19 to 30 months No alteration in the T 1/2 values was found

In four patients the turnover rate before and after Melphalan (l phenylalanine mustard) therapy was determined In 2 of these cases Melphalan had no effect upon the T 1/2, while in the other 2 the half-life changed from 9 2 to 13 9 days and from 16 1 to 19 6 days respectively The findings are discussed

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A Report on Two Adult Patients with Glycogen Storage Disease

By

P J Brombacher, S van Creveld, J P Damme, F Huijing and J F Ploem

Since the first clinical description of a child with glycogen storage disease by van Creveld (1) much fundamental work has been added since 1952, especially by the Coris (3) to the knowledge of enzymatic disturbances which can occur in this disease For a survey of this subject we may refer to the review published by one of us (5 6) Up till now we have been able to distinguish six different types of glycogenosis, nevertheless there are still many unsolved problems and in many aspects we are quite unaware about enzymatic aberrations which may exist in patients with glycogenosis who reached adult age So it seems justifiable to report on two such cases

Methods

Glucose (reduction) was determined by the method of Folin and Wu true glucose was determined with glucose oxidase (Boehringer test) Glycogen in blood or erythrocytes was determined in a trichloro-acetic acid extract after precipitation with alcohol with the anthrone method (8)

Lactate was determined with lactate dehydrogenase in principle as described by Hohorst (12) Dihydroxyacetone in blood was determined as decribed by Campbell (2) Phosphorylase and debranching enzyme (amylo-1,6 glucosidase) were determined as described by Huijing (15)

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Case reports

Case 1 In 1936 a 12 year-old girl was admitted to the department for Internal Medicine of the State University in Utrecht She had mechanical complaints about a big belly especially when stooping or sitting in a school bench This large abdomen had been noticed already in the first years of life but not until her tenth year did she begin to complain about it Quite remarkable was her everlasting hunger and her preference for fatty foods She never had any cramps or convulsions She has seven brothers and three sisters who are all in good health.

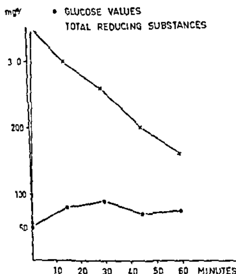


Fig 2 Case 1 Galactose loading test

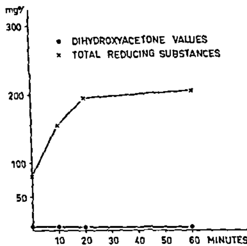


Fig 3 Case 1 Dihydroxyacetone loading test

disappearance of hepatomegaly on reaching adult age and increased uric acid content in the blood which was not accompanied by clinical signs of gout

Case 2 In 1961 a 39 year old woman was admitted to the department for internal medicine of the municipal hospital (»Weesper pleinziekenhuis») at Amsterdam A markedly enlarged liver had been found soon after birth She had been in other hospitals several times before In 1954 the diagnosis of glycogen in liver was established on biochemical investigations it was confirmed by microscopical examination of tissue obtained by liver biopsy before and after a period of fasting (Department of Medicine University of Amsterdam head Prof P Formijne M D

During childhood she had often been ill with complaints of headache shortness of breath and fatigue The menarche occurred at the age of 20

For the last 15 years the patient complained about pain and swelling of the joints as a result of severe arthritis urica Since hospitalization in 1954 she was successfully treated with benemide which drug during the last years however she used quite irregularly and in too small doses Thereupon the joint symptoms returned especially in her feet wrists and sterno-costal joints Moreover she began to suffer from facial aching resulting from frontal sinusitis for which condition she was treated in vain by puncture therapy of the sinuses

The complaints of joints and face led to her admission in 1961

On physical examination we saw a pale feeble minded woman looking much older than she was Arterial blood pressure was 110/75 mm Hg the pulse was regular and equal with a frequency of 96/min her length was 148 cm and her weight *50 0 kg* She was physically and psychically under developed

The heart was not enlarged a grade two systolic murmur could be heard over all ostia no pulmonary abnormalities were found On the skin of the abdomen light brown areas of pigmentation were seen The edge of the liver which was rather firm not tender and palpable four finger breadths below the right costal margin. The spleen was *not* palpable Of the extremities the big toes were deformed especially on the

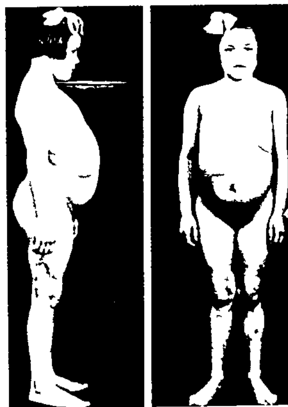


Fig 1 Case 1 Girl 12 years of age

There is no consanguinity between the parents

Physical examination revealed a girl with normal physical development, body length 131 cm, weight 34,2 kg (fig 1) Her breath had an acetone odour there were no muscular abnormalities At percussion the heart showed normal dimensions The edge of the liver was hard and smooth and could be felt till just over the umbilicus The spleen was not palpable No other abnormalities were found

Laboratory data In the urine no reducing substances were found acetone was always present Fasting blood sugar values were between 48 and 70 mg% After subcutaneous administration of 0 2 mg of epinephrine there was no rise in blood sugar values during two hours (fasting value and values 15, 30 45, 90 and 120 minutes were after injection respectively 56 59 60 55 and 57 mg%), normally there is a rise of 40—60 mg %

X ray examination of chest and abdomen, heart and kidneys proved to be normal

Re examination 25 years later We lost contact with the patient till we saw her again at the age of 37 In the meantime she was married and had two healthy children Menarche began at the age of 19 She came to our department because of diffuse abdominal complaints Her former preference for fatty foods had disappeared in the course of years

On physical examination a smooth liver edge one finger below the right costal margin could be felt Her weight was 63 1 kg, her length was 161 cm, arterial blood pressure was 110/65 mm Hg, no other abnormalities were found

Laboratory data In the urine neither reducing substances nor acetone were found Fasting blood sugar values were between 50 and 88 mg% After subcutaneous administration of 0 25 mg of epinephrine no rise in blood sugar values was seen (fasting value and values after 15, 30, 45 and 90 minutes were respectively 56, 59, 60, 60 and 55 mg%), this time, however, acetone was found in the urine

After intravenous administration of 1 19 mg glucagon (i e 0 7 mg/sq m body surface) no rise in the reducing substances in the blood or in blood lactic acid was seen, acetone appeared in the urine

Intravenous administration of 1 g galactose per kg body weight caused a significant rise of true glucose of the blood, galactose was injected as a 20 % solution within three minutes (fig 2)

Oral administration of 1 g dihydroxyacetone per kg body weight gave no rise in blood dihydroxyacetone values (fig 3), (7)

Serum cholesterol value was normal (190 mg/100 ml), total lipids slightly raised (845 mg/100 ml), uric acid level was found to be elevated 7 4 mg% the thymol turbidity test was elevated, bromosulphalein retention after half an hour was 8 %

On X-ray examination the heart was found to be normal no electrocardiographic deviations were found

Remarkable facts in this patient are her preference for fatty food for many years,

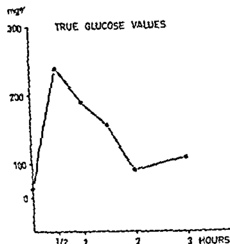


Fig 5 Case 2 Glucose loading test

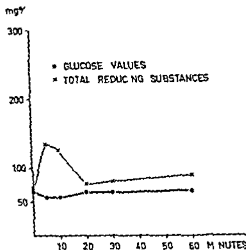


Fig 7 Case 2 Galactose loading test

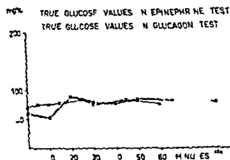


Fig 6 Case 2 Epinephrine and glucagon tests

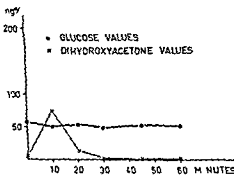


Fig 8 Case 2 Dihydroxyacetone loading test

In pat ent l we saw a rise in the blood gl ico e level after intravenous adm n istrat on of galacto e wh ich means th at galactose s tran formed nto gl cose via gl e 6-pl osphate by the act on of gl cose 6-pl osphata e 18 After in t a e a lm n trat on f glucagon no r e the blood lact c ac d level was see 0 O a co nt of these f nd ngs we th k type I f glycogen d ea e can be ex l led n o r f rst a e

We m a t conclu le th at pat ent 2 is s ffer ng f om type I glycoge os s A strong argument in favour of this d agnos s is the glucose 6-pl osphatase deficiency as found by the intravenous galactose experiment (fig 7) th is test be ng abnormal only in type I of the d ease 18) The pract cally unchanged blood gl cose val ues after injection of gl agon and ep nepl rine agree with th s type of gl cogenos s

Type II or Pompe s d ease or gen eralized gl cogenos s due to deficiency of the l sosomal enzyme alpha glu cos da e 11) — and type V or McArd



Fig 4 Case 2 Woman 39 years of age

left side with distinct limitation of motility Of the fingers several joints were deformed and also showed limitation of motility Both knees and shoulder joints produced distinct crepitations on movement

X ray examination of the hands showed a big round erosion in the distal part of the middle phalanx of the first finger of the right hand with heavy destruction of the second interphalangeal joint

In the feet the first metatarsophalangeal joint of the left foot showed arthritic changes and in the right foot serious destruction (fig 4) Both knees showed distinct arthritic changes with narrowing of the interarticular space of the left knee

Laboratory data In the urine glucose acetone and acetoacetic acid were absent Fasting blood glucose levels varied from 45—75 mg% fasting lactate levels from 79—84 mg% (normal values 10—15 mg%)

Blood cholesterol was high 620 mg% total lipids however were normal Uric acid content was increased (7 3—9 9 mg%) Blood values for bilirubin alkaline phosphatase thymol turbidity test and total protein (7 5 g%) content were found to be normal α_2 globulin content was moderately increased (1 8 g%) whereas γ globulin content was slightly decreased (1 1 g%)

We went through the following tests to determine the nature of her carbohydrate metabolism

a) Oral administration of 50 g glucose starting at a low fasting blood glucose level we saw a rapid rise to highly elevated values followed by a quick fall No glucose was excreted in the urine (fig 5)
b) Blood glucose values were only very little raised after subcutaneous administration of 0 5 mg epinephrine (fig 6)
c) Intravenous injection of 0 7 mg glucagon/sq m body surface produced only a slight elevation of the blood glucose level (fig 6), at the same time a rise of blood lactate was seen (from 56 mg% to 96 mg%)
d) Intravenous administration of 1 g/galactose/kg body weight (given within three minutes as a 20 % solution) showed a rapid increase and subsequent decrease o the content of total reducing sugars in the blood as the true glucose levels did not rise these rapid variations must be ascribed to the blood galactose content. This experiment therefore gave normal values for this patient (fig 7)
e) After oral administration of 1 g of dihydroxyacetone/kg body weight a considerable increase of blood DHA levels occurred followed by a rapid decrease pointing to a utilization of the triose The lactate values showed a temporary increased level (from 84 to 103 mg%) and blood glucose levels remained constant (fig 8)
f) A very high fasting value for the blood lactate content was invariably found (56—96 mg%)

Discussion

As regards the type of glycogenosis existing in the two patients we must distinguish six types of glycogenosis (table I) each caused by the deficiency of one enzyme The glycogen metabolism is depicted in fig 9 In type I the hepatomegalic or hepatorenal type, there is a deficiency or absence of glucose-6-phosphatase (3)

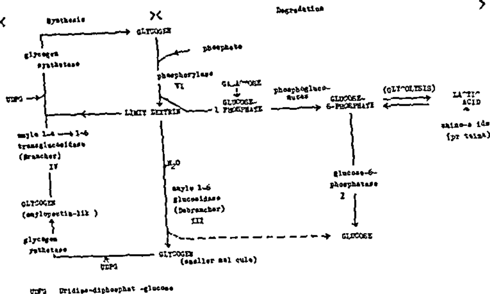


Fig 9 Glycogen metabolism

ing enzyme deficiency, seems unlikely in our patients because no serious liver function disturbances are found and the glycogen isolated from the blood, dissolved normally in water

Recently we have been able to differentiate between types III and VI without doing liver biopsy

Hulsmann et al (16) found that in type VI not only liver phosphorylase but also leucocytephosphorylase is diminished This was confirmed by Williams and Field 21) Furthermore one of us 15) found that amylo-1 6-glucosidase debranching enzyme) is present in normal leucocytes but absent in leucocytes of patients with amylo-1 6-glucosidase deficiency in the liver Increased levels of glycogen in the erythrocytes (18a) and the blood can be used as an indication for the existence of type III glycogenosis

In patient 1 a normal leucocyte phosphorylase activity was found The glycogen content of the erythrocytes and of the total blood was elevated the glycogen dissolved normally in water Amylo-1,6-glucosidase was completely absent in the leucocytes

Thus in patient 1 we have to do with type III glycogenosis Hers (11) divides this type into two subtypes one with complete absence of amylo-1,6-glucosidase in liver and muscle and one with complete absence in liver and partial deficiency in muscle At present we cannot decide to which subgroup our patient belongs

Prognosis of type III glycogenosis is favourable The exact moment of the disappearance of hepatomegaly in our patient is unknown In two adult patients of type III this occurred round puberty

TABLE I Diseases of glycogen storage

Type	Organs affected	Glycogen structure	Enzyme missing	Glucagon test	Adrenaline	Intra venous galactose test
I	Liver, kidneys	Normal	Glucose 6 phosphatase	No rise of blood sugar	No rise of blood sugar	No transformation into glucose
II	Cardiac type (glycogen in all tissues)	Normal	α Glucosidase (Hers)	—	Normal	—
III	Liver, muscle, heart ("Limit dextrinosis") (3)	Short outer branches	Debranching enzyme amylo 1 6 glucosidase	No rise of blood sugar after long fasting (rise in blood sugar in non fasting state)	No rise of blood sugar after long fasting (slight rise of blood sugar in non fasting state)	Normal
IV	Liver, retic endoth syst (liver cirrhosis)	Long outer branches	Branching enzyme? amylo 1, 4→1 6 transglucosidase	—	—	—
V	Muscles (partly resembling amyotonia congenita)	Normal	Phosphorylase in skeletal muscle	—	—	—
VI	Liver	Normal	Phosphorylase in liver	No or only slight rise of blood sugar	Slight rise of blood sugar in 1st 30 minutes or normal	Normal

le's disease, due to deficiency of phosphorylase in muscle, need not to be considered here as there existed no enlargement of the heart or muscular weakness

In type III there is storage of abnormal structured glycogen in liver and often also in heart and muscles, in this type there is an amylo 1,6 glucosidase (debranching enzyme) deficiency

In type VI there is a marked deficiency of liver phosphorylase and normal values for glucose-6-phosphatase and amylo-1,6 glucosidase (9)

The existence of the rarely described type IV (1) assumed to be due to branch-

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Biochemical Studies in Familial Cardiomyopathy

With Special Reference to the Differential Diagnosis from Known Types of Glycogen Storage Disease

By

P A Öckerman and S.-O Berlin

Familial cardiomyopathy is a disease of unknown etiology probably inherited as an autosomal dominant trait. Isolated reports occurred already 30 years ago (5, 21). After the description by Evans in 1949 (12) of a number of cases of this disease it has been described with increasing frequency (2, 3, 7—9, 13—17, 21—25, 27). This and the fact that during the past few years we have seen about 25 cases in two as yet incompletely examined families indicates that familial cardiomyopathy may not be an exquisite rarity.

The diagnosis of familial cardiomyopathy (7, 27) is based on clinical picture, heredity and findings of the pathologist. The clinical picture is characterized by disorders of heart rhythm, attacks of dizziness or syncope, sometimes exertional dyspnea, enlargement of the heart and ECG abnormalities, often with conduction changes. Clinically latent cases occur. Cases of similar heart disease or sudden, unexplained death occur in relatives. At autopsy a considerable enlargement of the heart is usually seen. The myocardium shows fibrosis and giant muscle fibers with vacuoles.

The most accepted current theory about the etiology of the disease is that it seems to be an isolated metabolic disorder of the myocardium. Battersby and Glenner (2) and Barry and Hall (1) showed accumulation of polysaccharides in the myocardium of cases with familial cardiomyopathy. In some reports a marked storage of glycogen in the myocardium was found (2, 11, 12, 15—17, 21) and the possibility that familial cardiomyopathy is a type of glycogen storage disease was discussed. The rapid development during the past few years of enzymic methods for the diagnosis of glycogen storage diseases (18, 20) has given a more solid basis for the judging of a possible connection between familial cardiomyopathy and glycogenosis. To

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At special examination we found in patient 2 normal values for total blood glycogen content and erythrocyte glycogen content and normal activity of leucocyte phosphorylase This is also in accordance with the diagnosis type I of glycogenosis in this patient

It is interesting that both patients showed high uric acid content of the blood but that only patient 2 had complaints of gout There may be some association between hyperuricaemia and glycogen storage disease (13, 14, 17)

Summary

Two adult female patients with glycogen storage disease, which was extensively studied with an interval of many years, are described

In the first patient the originally very big liver had decreased in volume There still existed important abnormalities in the metabolism We concluded after thorough biochemical investigation that in this case type III glycogen storage disease, debranching enzyme deficiency, exists

The second patient has still an enlarged liver as well as clinical and roentgenological symptoms of gout Here also exist important abnormalities in the carbohydrate metabolism, due to glucose-6 phosphatase deficiency So this is type I glycogen storage disease

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Fig 2 Pedigree of family II ○ Female □ Male ● Cardiomyopathy ◑ Probable cardiomyopathy ⊘ Not investigated ◯ Dead not investigated + Five children incompletely investigated ++ Eleven children not investigated

Fig 3 Some typical ECG The abnormalities are described in the text A Case I 1 B Case I 2 C Case I 3 D Case II 1 E Case II 2

pathological and a diagnosis of glycogen storage disease of the heart was considered likely ECG (Fig 3 C) revealed *deformed* and very broad ventricular complexes hyperexcitability and hypertrophy of both heart ventricles. The patient died following an Stokes-Adams attack. Post mortem examination showed a massively enlarged heart (weight 825 g) with a 3 × 3 cm fibrotic patch in the interventricular septum Valves and ostia were largely without changes Coronary arteries were normal Microscopically the *following* changes were seen *Pronounced* hypertrophy and vacuolisation *of the* muscle fibers with a moderate amount of glycogen (the specimen was fixed in both formalin and alcohol 24 hours after death) Fibrotic patches were seen Determinations of glycogen and enzymes were performed on postmortem material from heart and liver



Fig 1 Pedigree of family I ● Female, ■ male, with cardiomyopathy, [■ Male with probable cardiomyopathy, ⊗ Female, dead, not investigated

our knowledge biochemical studies in familial cardiomyopathy have not been performed earlier Using modern enzymic methods we analyzed autopsy and biopsy material from five patients of two different families with familial cardiomyopathy in order to find out if these patients show the same enzyme deficiency as in some known form of glycogenosis One of our patients had such a pronounced storage of glycogen in the myocardium that glycogen storage disease of the heart was considered to be the most probable diagnosis The results here presented do not establish the etiology of familial cardiomyopathy but show that, in the families studied by us, the disease is not identical with any known type of glycogen storage disease

Material

Our patients belong to two different families (figs 1—2) with at least 21 cases of heart disease showing the characteristics of familial cardiomyopathy concerning the clinical picture, heredity and findings at autopsy Some typical ECG's are shown in fig 3 Cogent support is lacking for the diagnosis of myocarditis, generalized muscular disease apparent neurological disorder and rheumatic or congenital valvular disease of the heart Several of the cases were thoroughly examined at cardiological departments but no definite diagnosis could be established Determinations of glycogen and enzymes were performed on muscle biopsies from four cases and on myocardium and liver from autopsy in one case The clinical data of these five patients will be summarized here

FAMILY I (fig 1)

Case 1 Female, 39 For more than one year this patient had had repeated short attacks of dizziness At the physical examination bradycardia, arrhythmia and a systolic murmur grade 2 over the whole precordium was noted X ray examination showed an enlarged heart (515 ml/m² body area) The enlargement included the left atrium and probably also both ventricles ECG was definitely pathological (fig 3A) with pronounced sinus arrhythmia, bradycardia, split and broad QRS complexes, high and broad P waves, peaked over the right half of the heart A muscle biopsy from the quadriceps femoris showed a normal microscopical picture Glycogen and enzyme determinations were performed on this biopsy specimen

Case 2 Female, 29 No symptoms Nothing remarkable in the physical status X ray examination demonstrated slight enlargement of the left atrium and bulging of the pulmonary artery Heart volume 320 ml/m² body area The lungs were normal ECG (fig 3B) showed high, peaked P waves especially in the precordial leads somewhat shortened PQ interval and inverted or diphasic T waves over the right part of the heart A biopsy taken from the quadriceps femoris showed a normal histological picture A sample from this muscle biopsy was taken for determination of glycogen and enzymes

Case 3 Male died at the age of 21 Attacks of paroxysmal tachycardia from the age of 17 About a month before death repeated Stokes Adams attacks A pace maker was implanted and at this operation a biopsy was taken from the left heart auricle The sample was fixed in formalin, but nevertheless the microscopic slides showed a pronounced storage of glycogen in the myocardium (fig 4) The accumulation of glycogen and the structural changes were considered definitely

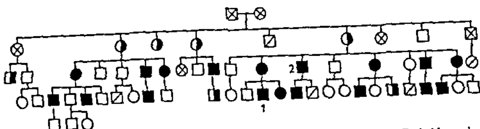


Fig. 2. Pedigree of family II. ○ Female □ Male ● Cardiomyopathy ◑ Probable cardiomyopathy ⊘ Not investigated ⊗ Dead, not investigated + Five children incompletely investigated ++ Eleven children not investigated.

A B C D E

Fig. 3. Some typical ECG. The abnormalities are described in the text. A Case I 1, B Case I 2, C Case I 3, D Case II 1, E Case II 2.

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Case 3 Male, died at the age of 21 Attacks of paroxysmal tachycardia from the age of 17 About a month *before* death repeated Stokes Adams attacks A pace-maker was implanted and at this operation a biopsy was taken from the left heart auricle The sample was fixed in formalin, but, nevertheless the microscopic slides showed a pronounced storage of glycogen in the myocardium (fig 4) The accumulation of glycogen and the structural changes were considered definitely

TABLE I Glycogen and enzyme analyses in four cases of familial cardiomyopathy The normal values for all enzymes measured are not definite and some of them are calculated from a very small series of assays They are in good accordance with those given by Hers (20)

Patient sex age	Material studied	Glycogen (% of wet weight)	α glucosidase[1]	Phosphorylase[2]	Amylo-1 6 glucosidase[1]	Glucose 6-phosphatase[2]
I 1 ♀ 39	M quadriceps fem[4]	1.70	0.187	100	0.67	—
2 ♀ 29	M quadriceps fem[4]	1.79	0.140	135	0.70	—
3 ♂ 21	Heart[3]	0.46	0.618	17.5	0.22	—
	Liver	0.73	1.47	31.0	0.69	1.07
II 1 ♂ 15	M obl int abdom[4]	1.09	0.115	61	0.44	—
2 ♂ 41	M quadriceps fem[4]	1.15	0.097	67	0.67	—
Normal values	Skeletal muscle	<2.0	[5]0.08–0.15	60–140	0.2–0.7	0
	Liver	<5.0	1.0 –2.3	15–50	0.4–1.1	4–13

[1] Expressed as μM glucose liberated per g wet weight per minute
[2] Expressed as μM phosphorus liberated per g wet weight per minute
[3] Material taken 24 hours post mortem
[4] Biopsy
[5] Probably higher for heart muscle

after death and analyzed after storage for about two years in the deep-freeze

For the homogenization of tissues and for the assay of *glycogen phosphorylase* and α glucosidase methods were used as described by Hers (18 19) Amylo-1 6-glycosidase was *measured with the limit* dextrin method as described by Hers (20)

Results

In table I the results of the determinations of glycogen and enzymes are summarized They should be compared with results found *in known types of* glycogenosis schematically outlined in table II

In the myocardium from case I 3 no glycogen increase was detectable after repeated chemical analyses performed on tissue from various parts of the myocardium (autopsy material) in accordance with the histological results on autopsy tissue The latter finding was *in contrast* to the histological results on biopsy tissue from the left heart auricle showing a considerable accumulation of glycogen (fig 4) The decreased activity of glucose 6-phosphatase in the liver can probably be explained as an *autolytic*, post mortem inactivation The value noted is, however, high enough to indicate a definite activity of this enzyme Therefore, type 1 glycogenosis can be excluded because this type of glycogenosis with the method used shows a total lack of activity of glucose 6-phosphatase (18) (table II) The distinct activity of α glucosidase found in both liver and myocardium makes it possible to exclude type 2 glycogenosis (Pompe's disease) (19) Likewise other muscle glycogenoses (types 3 and 5) can be ruled out since these diseases have a

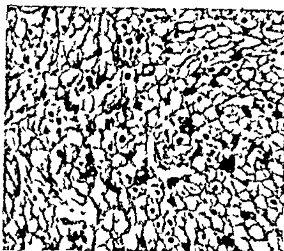


Fig 4 Biopsy from the left heart auricle of case I 3 Fixed in formalin Best s carmine Marked vacuolization of muscle fibers at least in part due to the storage of glycogen

taken 24 hours after death This patient has been discussed by Elmqvist et al (ref 10, case 13)

FAMILY II (fig 2)

In this family at least 18 cases have been found Two of these died during Stokes-Adams' attacks at the age of 42 and 27 respectively (mother and son) Autopsy showed septal fibrosis Five more patients died of heart disease, but the diagnosis is insufficiently confirmed because of lack of detailed information One of these died during an Stoke Adams attack at the age of 48 Several cases are clinically latent (For further details on family I and II see Berlin et al (4) In this paper two members of family II are discussed

Case 1 Male 15 In 1954 when the patient had poliomyelitis, a systolic murmur and slight enlargement of the heart was noted ECG showed slight left heart dominance and elevation of the ST segment In 1959 he was examined in a cardiological department No definite diagnosis was established In March 1962 he was again examined by the cardiologists who found a systolic click over the whole heart and a systolic murmur grade 3 with maximal intensity over the second interstitium mid sternal The second tone was split without pathological accent ECG (fig 3 D) showed incomplete bundle branch block with Wolff Parkinson White syndrome Catheterization of the heart with angiocardiography gave a slight suspicion of a mild aortic stenosis, but there was no definite evidence of that diagnosis The patient had felt tired for some years and had difficulties in managing his work as an upholsterer s apprentice At times he had headache and pains over the heart Six days after an operation for perforated appendix (Sept 1962) he had an attack of paroxysmal tachycardia which could be stopped with digitalis Since this he has had repeated attacks of paroxysmal tachycardia At the operation for appendicectomy a biopsy was taken from the obliquus internus abdominis muscle for assay of glycogen and enzymes

Case 2 Male, 40 Admitted to hospital six times 1957—63 for intoxication with barbiturates Treated at a mental clinic 1958 Since the age of about 20 non-characteristic precordial pain, in the latter years mainly following effort ECG 1956 revealed myocardial lesion with inverted T in several leads Clinical examination of the heart 1963 showed no definite abnormality except moderate cardiac enlargement X ray examination showed a volume of 630 ml/m² body area and a left ventricular enlargement No definite signs of heart failure were noted B P was 140/85 ECG 1963 Heart rate 50 regular sinus rhythm, split but not enlarged P waves, PQ 0 10 sec, split QRS, especially in lead III, ST depression in leads I—III, T inverted in I, II and V 3—7 (fig 3 E) A biopsy was taken from the quadriceps femoris for assay of glycogen and enzymes Histologically the muscle tissue obtained was normal

Methods

The muscle biopsies from cases I 1, 2 and II 1 2 were immediately frozen on dry ice and stored for a few days at — 20° C before the analyses were performed The autopsy material from case I 3 was frozen 24 hours

TABLE I Glycogen and enzyme analyses in four cases of familial cardiomyopathy The normal values for all enzymes measured are not definite and some of them are calculated from a very small series of assays They are in good accordance with those given by Hers (20)

Patient sex age	Material studied	Glycogen (% of wet weight)	α glucosidase[1]	Phosphorylase[2]	Amylo-1 6 glucosidase[1]	Glucose 6 phosphatase[2]
I 1 ♀ 39	M quadriceps fem [4]	1 70	0 187	100	0 67	–
2 ♀ 29	M quadriceps fem [4]	1 79	0 140	135	0 70	–
3 ♂ 21	Heart[3]	0 46	0 618	17 5	0 22	–
	Liver[3]	0 73	1 47	31 0	0 69	1 07
II 1 ♂ 15	M obl int abdom [4]	1 09	0 115	61	0 44	–
2 ♂ 41	M quadriceps fem [4]	1 15	0 097	67	0 67	–
Normal values	Skeletal muscle	<2 0	[5]0 08–0 15	60–140	0 2–0 7	0
	Liver	<5 0	1 0 –2 3	15–55	0 4–1 1	4–13

[1] Expressed as μM glucose liberated per g wet weight per minute

[2] Expressed as μM phosphorus liberated per g wet weight per minute

[3] Material taken 24 hours post mortem

[4] Biopsy

[5] Probably higher for heart muscle

after death and analyzed after storage for about two years in the deep freeze

For the homogenization of tissues and for the assay of glycogen phosphorylase and α glucosidase methods were used as described by Hers (18 19) Amylo-1 6 glycosidase was measured with the limit dextrin method as described by Hers (20)

Results

In table I the results of the determinations of glycogen and enzymes are summarized They should be compared with results found in known types of glycogenosis schematically outlined in table II

In the myocardium from case I 3 no glycogen increase was detectable after repeated chemical analyses performed on tissue from various parts of the myocardium (autopsy material) in accordance with the histological results on autopsy tissue The latter finding was in contrast to the histological results on biopsy tissue from the left heart auricle showing a considerable accumulation of glycogen (fig 4) The decreased activity of glucose 6 phosphatase in the liver can probably be explained as an autolytic, post mortem inactivation The value noted is, however high enough to indicate a definite activity of this enzyme Therefore, type 1 glycogenosis can be excluded because this type of glycogenosis with the method used shows a total lack of activity of glucose 6-phosphatase (18) (table II) The distinct activity of α glucosidase found in both liver and myocardium makes it possible to exclude type 2 glycogenosis (Pompe s disease) (19) Likewise other muscle glycogenoses (types 3 and 5) can be ruled out since these diseases have a

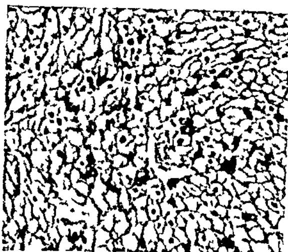


Fig 4 Biopsy from the left heart auricle of case I 3 Fixed in formalin Best s carmine Marked vacuolization of muscle fibers, at least in part due to the storage of glycogen

taken 24 hours after death This patient has been discussed by Elmqvist et al (ref 10, case 13)

FAMILY II (fig 2)

In this family at least 18 cases have been found Two of these died during Stokes-Adams' attacks at the age of 42 and 27 respectively (mother and son) Autopsy showed septal fibrosis Five more patients died of heart disease, but the diagnosis is insufficiently confirmed because of lack of detailed information One of these died during an Stoke Adams attack at the age of 48 Several cases are clinically latent (For further details on family I and II see Berlin et al (4) In this paper two members of family II are discussed

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Methods

The muscle biopsies from cases I 1 2 and II 1 2 were immediately frozen on dry ice and stored for a few days at — 20 C before the analyses were performed The autopsy material from case I 3 was frozen 24 hours

TABLE III Clinical differential diagnosis between muscle and heart glycogenoses and familial cardiomyopathy

	Glycogenoses			Familial cardiomyopathy
	Type[1] 2	Type 3	Type 5	
Mode of inheritance	Recessive	Recessive	Recessive	Dominant
Age at onset of symptoms (years)	Infancy	Childhood	Childhood	5—60 (varying)
Age at death (years)	0—1(2)	(Childhood) Usually not fatal	Not fatal	10—60 (varying)
Cardiomegaly	Marked (with a few exceptions)	Usually not detectable	Not proven	None to marked
Hepatomegaly (of non-circulatory origin)	Moderate	Moderate to marked (during childhood)	None	None
Muscle weakness	Moderate to severe	None or moderate	Severe intolerance for work	None or moderate (severe)
Cretinism or mongol facies	Occurs	None	None	None
Macroglossia	Occurs	None	None	None
Neurological symptoms	Occur	None	None	None
ECG changes	Marked	Usually none	None known	Marked
Affected organs	Generalized	Liver muscles heart (?) kidneys (?)	Muscles (heart?)	Heart muscles
Glycogen storage organs	Generalized	Liver muscles heart (?) kidneys (?)	Muscles (heart?)	Heart muscles (inconstant)

[1] Pompe's disease

one of our patients (case I 3) he became the starting point of this study The immediate problem was to decide whether our cases of familial cardiomyopathy show a pecific genetically determined enzyme deficiency of any of the types described in glycogen storage disease

The opinions on the occurrence and significance of myocardial glycogen accumulation in cases of familial cardiomyopathy are highly divergent Gaunt and Lecutier (16) consider the storage of glycogen in myocardium and skeletal muscles to be the most important pathological change in cases of familial cardiomyopathy On the other hand many authors deny the existence of any indication of a pathological storage of

TABLE II Types of hereditary glycogen deposition disorders (classification modified and simplified after Hers (20), and Brante, Kayser & Öckerman (6)

Type	Enzyme defect	Storage organ	Glycogen structure	Suggested clinical name
1	Glucose 6 phosphatase	Liver, kidney	Normal	Glucose 6 phosphatase deficiency
2	α glucosidase	Generalized	Normal	α glucosidase deficiency generalized glycogenosis Pompe s disease
3	Amylo 1,6 glucosidase (debrancher)	Liver and muscle	Abnormal missing or very short outer branches	Debrancher deficiency limit dextrinosis
4	Amylo-(1,4→1 6)-transglucosidase(?) (brancher) Plasma amylase?	Liver probably other organs	Abnormal, long inner and outer branches	Amylopectinosis
5	Muscle phosphorylase	Muscle	Normal	Myophosphorylase deficiency glycogenosis
6	Liver phosphorylase (?) (Activity present but lowered not in all cases, however)	Liver	Normal	Hepatophosphorylase deficiency glycogenosis

total lack of activity of amylo-1,6-glucosidase and myophosphorylase, respectively (table II)

As regards cases I 1, 2 and II 1, 2 the same reasoning can be applied glycogenosis of types 2, 3 and 5, i e all known muscle and heart glycogenoses can definitely be excluded (tables I and II) The level of glycogen in the muscle biopsies in all four cases falls within normal limits Biochemical criteria for the diagnosis of known types of muscle and heart glycogenoses are thus lacking in all five cases examined

Discussion

The patients studied here belong to families where several members show characteristics well in accordance with earlier described cases of familial cardiomyopathy regarding heredity, clinical picture, ECG and findings at autopsy Since specific diagnostic methods are lacking, other disorders must be considered, especially certain hereditary diseases that can affect the myocardium, such as Friedreich's ataxia and muscular dystrophy (7, 26, 27), as well as myocarditis Available data speak against these diagnoses in our series (4)

A diagnosis of glycogen storage disease has been discussed in such cases of familial cardiomyopathy, where a pathologically increased storage of glycogen in the myocardium has been found (2, 11, 12, 15—17, 21) Since this was true of

separated from all known forms of glycogenosis by means of biochemical analysis

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glycogen in their cases (3, 8, 13, 14, 23, 24)

From the *clinical* point of view there is little support for a diagnosis of glycogenosis in cases of familial cardiomyopathy The clinical progress of glycogen storage disease of the heart (type 2 or Pompe's disease, see table III) is usually different from that of familial cardiomyopathy, e g patients with Pompe's disease are known to die within the first few years of life As illustrated in table III, a clinical differential diagnosis between cardiomegalic glycogenosis (Pompe's disease) and familial cardiomyopathy of unknown genesis should be possible in most cases This has been realized by most authors, even those who found a pathological storage of glycogen in their patients, and thus they usually have considered that the two diseases are etiologically distinctly separated In the other forms of muscle glycogenosis usually no or very few symptoms or signs of heart disease are found (table III) Nevertheless, the discussions on a possible connection have continued and diagnostic problems have arisen

Our results show that familial cardiomyopathy, in the cases studied by us is not identical with any at present known form of muscle glycogenosis and that at least some cases of familial cardiomyopathy histologically may demonstrate a pathological storage of glycogen in the myocardium This glycogen is possibly easily catabolized post mortem There is no fully acceptable explanation for the occurrence of an increased storage of myocardial glycogen in certain cases of familial cardiomyopathy Possibly, it should be considered as an unspecific phenomenon

The biochemical analyses on biopsy material discussed here can be of decisive value for establishing the diagnosis in obscure cases of cardiomyopathy, in which a diagnosis of glycogen storage disease is considered

As in glycogenosis, the etiology of familial cardiomyopathy is probably a genetically determined metabolic defect, possibly an enzyme deficiency Our knowledge at present of its pathogenesis is practically none However interesting the accumulation of glycogen or other polysaccharides (1) in the myocardium, may be, it does not give the answer to the pathogenesis We believe that the problem will be solved by applying biochemical methods from other starting points and with new aspects

Summary

A relation between glycogen storage diseases and familial idiopathic cardiomyopathy has been discussed by several authors Recent developments in the enzymic diagnosis of glycogen storage diseases made it possible in five cases from two families with idiopathic cardiomyopathy to study this relation biochemically Although the histological diagnosis in one of the cases was glycogen storage disease of the heart, it could be shown that all five cases had distinct activities of all enzymes ordinarily found to be absent in the different known types of glycogenosis affecting muscle and heart This implies that the heart disease in the two families studied can be

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Papillary Muscle Rupture in Myocardial Infarction

A Study Based upon an Autopsy Material

By

Lars Cederqvist and Jan Soderstrom

Papillary muscle rupture is still regarded as a fairly rare complication of myocardial infarction This paper is concerned with an investigation of the frequency of such ruptures in a large necropsy series of acute myocardial infarction

Material and methods

The investigation covered a 5 year period (1957 to 1961) During this time 4741 patients above 29 years were examined post mortem at the Department of Pathology Malmo General Hospital Since the town is served by only one hospital for acute somatic diseases and since 98—99 % of all patients dying in hospital are necropsied the material lends itself well to statistical treatment (4 26 44) The protocols of all patients with myocardial infarction healed or acute were perused special attention being given to both the clinical and the pathological findings in cases with ruptured papillary muscles

Findings

The number of necropsies performed the incidence of acute myocardial infarctions and the frequency of papillary muscle rupture are given in table I Clinical data on cases of papillary muscle rupture are presented in table II and the pathological findings in table III The frequencies of the complication in published necropsy series are summarized in table IV

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Discussion

Papillary muscle rupture was first reported in 1803 by Merat (29) In 1957 Sanders (37) collected 58 cases from the literature to which he added 3 of his own We have traced a further 23 cases in the literature (1 3 5 6 7 12 16 17 20 28 43) to which we can add 5 cases seen in our department In Sanders compilation papillary muscle rupture was most frequently due to myocardial infarction (79 %) Other causes were trauma (14 22 34 35) syphilis (41) ulcerative endocarditis (15 42) and periarteritis nodosa (2)

Papillary muscle rupture has been reported much more frequently in recent years but it is not known whether the condition has really become more common or whether the increase should be

TABLE III Post mortem finding

	Case no				
	1	2	3	4	5
Extent of infarction in left ventricle	Post + lat wall	Post wall	Ant wall + septum	Ant + lat wall	Post wall + septum
Myocard rupt + haemopericard	–	+	+	–	–
Pap musc rupt relative to mitralis	Posterior	Posterior	Anterior	Posterior	Posterior
Coronary sclerosis	Severe	Severe	Severe	Severe	Severe
Occluded coronary artery	Left circumflex	Right coronary	Left descending	–	Right coronary
Heart weight (g)	730	320	590	300	315
Dilatation of left ventricle	+	–	+	(+)	–
Pulm oedema	+	–	+	+	+
Hydrothorax (ml)	1 400	–	1 600	100	500
Fluid in pericardium (ml)	–	300 blood	100 blood	–	30 clear fluid

TABLE IV Survey of published series

Author	Year	No of autopsies	Pap musc rupt secondary to myocardial infarction	
			No	%
Maurice et al (28)	1959	1 357	3	0 22
Harnischfeger & Denten (19)	1955	1 176	1	0 09
Kumlin & Seppäla (23)	1955	13 965	5	0 04
Craddock & Mahe (9)	1953	500	3	0 60
Ritama & Heino (36)	1953	2 300	3	0 13
Hackel & Kaufman (15)	1953	11 500	1	0 01
McKeown (27)	1949	5 000	2	0 04
Davison (10)	1948	14 000	3	0 02
Foster (13)	1946	2 915	1	0 03
Moragues (30)	1959	3 400	1	0 03
Total		56 139	24	0 04
Own material		4 741	5	0 11

TABLE I Survey of material (1957–1961)

	Men	Women	Total
Autopsies (>29 yrs)	2 373	2,368	4 741
Acute infarctions	342 (14 4%)	236 (10 0%)	578 (12 2%)
Rupture of papillary muscle	2	3	5 (0 865%)

TABLE II Clinical data on 5 cases of papillary muscle rupture secondary to myocardial infarction

	Case no				
	1	2	3	4	5
Age and sex	50♂	79♀	80♂	77♀	79♀
Approximate interval between infarction and rupture (days)	37	7	10	Some	2
Hypertension known	–	–	–	–	+
Retrosternal pain	+	+	+	+	+
Systolic murmur	+	–	?	?	+
Thrill	–	–	–	?	–
Pulm oedema	+	?	+	?	+
Probable survival after rupture	1 day	–	Some hrs	< 1 day	1 day
Antiprothrombin treatment	+	+	–	–	+
Prothrombin index at time of rupture	88	41			74

ascribed to wider interest in the complication It was therefore felt warranted to estimate the incidence of the papillary muscle rupture in a large representative necropsy series

In published series the condition was demonstrated in 0,04 % of all cases studied post mortem irrespective of the cause of death The corresponding figure for the present series was 0 11 % These figures are, however, hardly comparable because the series on which previous investigations were based were often not representative For example, only 4 authors (7, 13, 23, 28) reported the frequency of papillary muscle rupture relative to that of myocardial infarction (table V) Only one author (28) gave the number of acute infarctions separately

Spontaneous papillary muscle rupture was diagnosed for the first time *intra vitam* in 1948 (10), since when about 10 further cases have been described (2, 6, 17, 38, 39)

Papillary muscle rupture has been known to occur from a few hours (17) to some weeks (37) after the actual myocardial infarction The rupture is associated with severe retrosternal pain (2, 7 9, 10 11, 12 17 25 26, 27, 36 37, 38, 39, 40, 43) which usually radiates to the left shoulder and arm In half of all cases auscultation will also reveal

in 4 Two of our 5 cases also showed hemopericardium due to rupture of the wall of the heart, an extremely rare combination, which to our knowledge has been described previously in only one case (37)

Advances in heart surgery increasingly demand correct clinical diagnosis of myocardial infarction and its complications (6) A search of the literature, however failed to reveal a report of any successful operation of a ruptured papillary muscle in a patient with myocardial infarction But 2 cases are on record in which the operator succeeded in attaching a ruptured papillary muscle in the right ventricle in one case the rupture was due to trauma, in the other, to *endocarditis* (8)

Summary

In a 5 year necropsy series lending itself well to epidemiological studies, papillary muscle rupture was demonstrated in 0 9 per cent of all patients with acute myocardial infarction

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TABLE V Published necropsy series with data on frequency of papillary muscle rupture secondary to myocardial infarction

		No. of infarct		Pap. musc. rupt. secondary to myocardial infarction	
Author	Year	Total	Recent	No.	%
Maurice et al. (28)	1959	316	156	3	0.95
Buttenberg & Dolter (7)	1959	118	Not mentioned	1	0.86
Kumlin & Seppälä (23)	1955	595	Not mentioned	5	0.84
Foster (13)	1946	234	Not mentioned	1	0.43
Total		1,263		10	0.79
Own material		1,548	578	5	0.32

supervention of a systolic murmur (2, 9, 10, 19, 21, 24, 28, 32, 37, 38, 39, 40) or occasionally a diastolic murmur (6). Thrill does not occur with complete rupture of a papillary muscle (9, 17). Survivals up to 14 months (6) have been reported. The commonest direct cause of death is sudden pulmonary oedema secondary to left ventricular failure (2, 5, 7, 9, 10, 17, 18, 19, 24, 25, 27, 28, 30, 32, 36, 37, 38, 39, 42, 43). In differential diagnosis it should be borne in mind that a systolic murmur is also heard in interventricular septum rupture but is then loudest in the fourth or fifth left intercostal space (6, 37), and that a thrill can be felt in about half of all cases. A systolic murmur may also develop in cardiac dilatation associated with mitral insufficiency (11, 37) or in arrhythmia (11) both in the course of an infarction and with rupture of the mitral valves chordae tendineae of the mitral valves (33). But the latter condition is of little differential diagnostic interest since it rarely follows acute myocardial infarction.

In our 5 cases myocardial infarction had been diagnosed *intra vitam*, but rupture of a papillary muscle or of the interventricular septum had not been suspected. All of the patients had had severe retrosternal pain and all had died within one day from pulmonary congestion. In 2 cases a systolic murmur had been heard but no thrill had been felt.

Necrosis of papillary muscle in the left ventricle has been noted in 20 % of patients with myocardial infarction (31). The posterior papillary muscles rupture somewhat more frequently than the anterior (37).

In only one of our 5 cases had the rupture been preceded by known hypertension. In 4 it was the posterior papillary muscle that had ruptured and in one the anterior. All of the cases had extensive myocardial infarction and severe coronary sclerosis, with occlusion

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Studies on the Acute Effect of Guanethidine on the Free Fatty Acids of Plasma in the Dog

By

LARS ORO

It is now evident that lipids are mobilized from adipose tissue in the form of free fatty acids (FFA) (15, 22 32) This process is influenced by various hormones (27) Norepinephrine and epinephrine enhance FFA mobilization in vivo (15 20) as well as in vitro (19 27) During many conditions with increased activity in the sympathetic nervous system such as mental stress (5, 12) experimental trauma (10), cold exposure (18) and hypoglycemia induced by insulin (2 17), there is a rise of the FFA level in plasma which can be inhibited by sympathetic-blocking agents These and other findings suggest that the endogenous catechol amines are of importance for FFA mobilization in man and dog It is however not known if the mobilization is produced by a local release of the norepinephrine within adipose tissue (26 29) and/or produced by catecholamines from other sources outside adipose tissue

Endogenous catecholamines can also be actively released by different drugs as tyramine, which causes not only a blood pressure rise (33) but also an increase of FFA concentration in plasma in the rat (30) and dog (25) Guanethidine a sympathetic blocking agent which can inhibit the FFA mobilization during hypoglycemia (2) and experimental trauma (10), also has an initial sympathomimetic action on the circulation in the dog, probably due to a release of endogenous catecholamines (4, 21) The present investigation was performed to study the acute effect of guanethidine on FFA metabolism in the dog To elucidate the mechanism of the observed many fold rise of the FFA concentration produced by guanethidine, experiments were also carried out on adrenalectomized dogs and on dogs treated with a sympathetic blocking agent reserpine or phentolamine

It was recently demonstrated that nicotinic acid inhibited the catechol amine stimulated FFA mobilization in vivo (7, 16) as well as in vitro (8) To further study the effect of nicotinic acid on

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By

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It is now evident that lipids are mobilized from adipose tissue in the form of free fatty acids (FFA) (15 22 32) This process is influenced by various hormones (27) Norepinephrine and epinephrine enhance FFA mobilization in vivo (15, 20) as well as in vitro (19, 27) During many conditions with increased activity in the sympathetic nervous system, such as *mental stress* (5 12) experimental trauma (10) cold exposure (18) and hypoglycemia induced by insulin (2 17), there is a rise of the FFA level in plasma which can be inhibited by sympathetic-blocking agents These and other findings suggest that the *endogenous* catechol amines are of importance for FFA mobilization in man and dog It is however not known if the mobilization is *produced* by a local release of the norepinephrine within adipose tissue (26 28) and/or produced by catecholamines from other sources outside adipose tissue

Endogenous catecholamines can also be actively released by different drugs as tyramine, which causes not only a blood-pressure rise (33) but also an increase of FFA concentration in plasma in the rat (30) and dog (25) *Guanethidine* a sympathetic blocking agent which can inhibit the FFA mobilization during hypoglycemia (2) and experimental trauma (10), also has an initial sympathomimetic action on the circulation in the dog probably due to a release of endogenous catecholamines (4 21) The present investigation was performed to study the acute effect of guanethidine on FFA metabolism in the dog To *elucidate* the mechanism of the observed many fold rise of the FFA concentration produced by guanethidine, experiments were also carried out on adrenalectomized dogs and on dogs treated with a sympathetic blocking agent reserpine or phentolamine

It was recently demonstrated that nicotinic acid inhibited the catecholamine stimulated FFA mobilization in vivo (7 16) as well as in vitro (8) To further study the effect of nicotinic acid on

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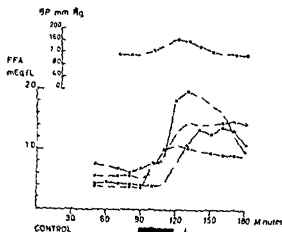


Fig 1 Effect of guanethidine on the free fatty acids of plasma (FFA) and the mean blood pressure (mean value) (BP) in 4 dogs Guanethidine (I) was administered as described in the text

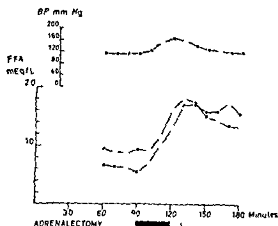


Fig 2 Effect of guanethidine on the free fatty acids of plasma (FFA) and the mean blood pressure (mean value) (BP) in 2 dogs adrenalectomized about 2 weeks before the experiments Guanethidine (I) was administered as described in the text

FFA metabolism, dogs were here also given nicotinic acid before the administration of guanethidine

Methods

Experimental Dogs weighing 15—27 kg were used After fasting overnight the dogs were anesthetized with an initial dose of Nembutal® (Abbott) 30 mg/kg body weight intravenously The blood pressure was measured continuously with an Elema Schonander pressure transducer (EMT 490 A) from a teflon catheter inserted into the femoral or brachial artery The blood pressure transducer was filled with saline and no heparin was injected into the animals In all series of experiments guanethidine was injected intravenously, 5 mg/kg body weight The total dose was divided into 12 portions, injected at 2 1/2 minute intervals

In the *first* series of experiments with 4 dogs only guanethidine was injected

In the *second* series of experiments 4 dogs were pretreated with reserpine Reserpine was injected intramuscularly about 48 and 24 hours before the experiments in a total dose of 0 6 to 0 8 mg/kg body weight All dogs become markedly sedated by the reserpine treatment

In the *third* series of experiments with 4 dogs, phentolamine, 4 mg/kg body weight, was injected intravenously 30 minutes before the administration of guanethidine

In the *fourth* series of experiments with 4 dogs, nicotinic acid was injected intravenously, in a dose of 200 mg/kg body weight 20 minutes before the administration of guanethidine

Two dogs were adrenalectomized by S O Liljedahl (Associate Professor of Surgery) They were given substitution therapy with cortisone acetate intramuscularly, 1—2 mg kg body weight daily, and appeared healthy The experiments were performed about two weeks after the operations Since the reserpine treated and the adrenalectomized dogs were abnormally sensitive to anesthesia only 5 to 10 mg/kg body weight of Nembutal® was given as a initial dose

Substances Guanethidine (Ismelin) reserpine (Serpasil®) and phentolamine (Regitin®) were kindly supplied by AB Ciba Stockholm Nicotinic acid was given as the sodium salt in solution at pH 7, 20 g 100 ml

Analytical Arterial blood samples were withdrawn into heparinized syringes and centrifuged immediately The FFA were determined according to Dole (13) Addition in vitro of the investigated substances in concentrations exceeding the calculated maximal

TABLE I The effect of guanethidine on the FFA concentration (mEq/l) in the dog The figures are calculated from the individual changes in concentration based on that immediately before the administration of guanethidine and represent the mean values (MV) and the standard errors of the mean (SEM) All dogs received 5 mg/kg body weight of guanethidine

		Min after start of guanethidine administration					
		10	20	30	40	50	60
Controls (4 dogs)	MV	0 13	0 31	[1]0 76	[2]0 90	[2]0 91	[2]0 83
	SEM	± 0 07	± 0 13	± 0 15	± 0 14	± 0 11	± 0 09
Re erpine 0 6 – 0 8 mg/kg (4 dogs)	MV	– 0 03	– 0 03	0 00	0 03	0 00	– 0 01
	SEM	± 0 02	± 0 04	± 0 06	± 0 08	± 0 07	± 0 05
Phentolamine 4 mg/kg (4 dog)	MV	0 ^6	0 26	0 3›	[2]0 50	[2]0 48	0 41
	SEM	± 0 05	± 0 10	± 0 11	± 0 10	± 0 13	± 0 14
Nicotinic acid 200 mg/kg (4 dog)	MV	0 Ƒ2	0 02	0 04	0 11	[2]0 16	[2]0 17
	SEM	± 0 03	± 0 02	± 0 02	± 0 0J	± 0 03	± 0 06
Adrenalectomy (2 dogs)	MV	0 08	0 35	0 69	1 02	1 03	0 ˜7

[1] $p < 0.05$ [2] $p < 0.01$

concentration in plasma in vivo did not influence the titration values

The glycerol concentration was determined in some experiments with the method described by Wieland (51)

Results

Effect of guanethidine on the free fatty acids of plasma and the blood pressure

The guanethidine administration produced a rise of the FFA concentration in all experiments (fig 1) As can be seen in table I this rise was statistically significant It was also evident that one hour after the end of the injection the concentration of FFA was still markedly elevated The blood pressure also increased in all experiments (fig 1) I: tw: of them tne glycerol concentration was determined and found to increase in parallel with the FFA concentration The maximal rise was from 0 056 to 0 147 and from 0 063 to 0 184 mMol/l respectively

Effect of guanethidine on the free fatty acids of plasma and the blood pressure in adrenalectomized dogs

Guanethidine raised the concentration of free fatty acids and the blood pressure in the two adrenalectomized dogs (fig 2) The changes were of the same order as in the control animals (table I) The glycerol concentration also increased parallel with the FFA concentration in the two dogs from 0 080 to 0 153 and from 0 069 to 0 193 mMol/l respectively

Effect of reserpine on the guanethidine induced changes in the free fatty acids of plasma and the blood pressure

When guanethidine was injected into dogs pre treated with reserpine there was a small rise of the FFA concentration only in one dog out of four (fig 3) The mean FFA concentration was unchanged (table I) The mean blood pressure did not increase during guanethidine administra

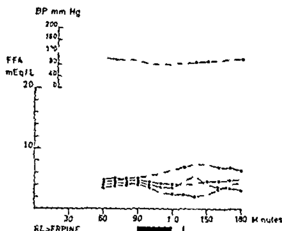


Fig 3 Effect of reserpine on the guanethidine induced changes of the free fatty acids of plasma (FFA) and the mean blood pressure (mean value) (BP) in 4 dogs Reserpine and guanethidine (I) were administered as described in the text

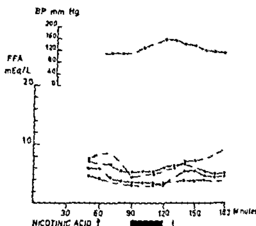


Fig 5 Effect of nicotinic acid on the guanethidine induced changes of the free fatty acids of plasma (FFA) in 4 dogs Nicotinic acid and guanethidine (I) were administered as described in the text

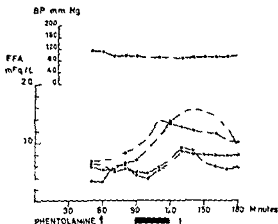


Fig 4 Effect of phentolamine on the guanethidine-induced changes of the free fatty acids of plasma (FFA) and the mean blood pressure (mean value) (BP) in 4 dogs Phenotolamine and guanethidine (I) were administered as described in the text

tion in the reserpine treated animals (fig 3) At the end of two experiments norepinephrine was infused at a constant rate of 0 6 µg/kg/minute during 20 minutes These infusions increased the FFA concentration from 0,41 to 2 34 and from 0 35 to 2 05 mEq/l respectively

Reserpine was also injected intravenously, as a single dose of 1 mg kg body weight, into two untreated animals No changes in FFA concentration were observed within three hours after the administration

Effect of phentolamine on the guanethidine-induced changes of the free fatty acids of plasma and the blood pressure

Guanethidine increased the concentration of FFA in all the phentolamin treated animals (fig 4) The mean rise was statistically significant (table I)

The guanethidine-induced blood pressure rise was inhibited in all dogs pretreated with phentolamine (fig 4)

Effect of nicotinic acid on the guanethidine induced changes of the free fatty acids of plasma and the blood pressure

In the dogs pre treated with nicotinic acid guanethidine produced only a small rise in FFA concentration (fig 5, table I) The mean rise in FFA concentration was significantly lower than in the control animals The mean blood pressure however increased as in the control animals (fig 5)

Discussion

In the present investigation it was found that acute intravenous injection of guanethidine into anesthetized dogs produced a several fold rise of the FFA level in plasma. This effect on FFA has previously been observed by Boshart and Ringler (6) and by Carlson and Liljedahl (10). The glycerol level also markedly increased, which suggested that the FFA concentration rise was due to an enhanced lipolysis and mobilization of FFA from adipose tissue (9).

To study the mechanism of the guanethidine induced FFA concentration rise, dogs were pre treated with reserpine before injection of guanethidine. It is now established that reserpine does not directly inhibit but often potentiates the effects of exogenously administered catecholamines and sympathomimetic agents (1, 33). The sympathetic blocking action of reserpine is explained by its ability to deplete the sympathetic nerves of catecholamines (33). The norepinephrine in adipose tissue also disappears after reserpine treatment (18, 28). Recent histochemical investigations (Wirsen, to be published) suggested that in adipose tissue there are only adrenergic nerves in connection with the vessels. Preliminary studies on dogs showed that the catecholamines completely disappeared in these nerves after treatment with reserpine in a dose like that used here. This treatment with reserpine also abolished the effect of guanethidine but not the effect of injected norepinephrine on FFA concentration and blood pressure. The results therefore strongly suggested that the effect of guanethidine on FFA and blood pressure was due to an active release of endogenous catecholamines.

This mechanism of action is also suggested by a previous report that guanethidine increased the concentration of catecholamines in plasma from the coronary sinus of heart after acute administration (21). However, it is not directly known if catecholamines are released from other tissues. As the adrenal medulla is an important source of circulating catecholamines during different conditions, experiments were performed on adrenalectomized dogs. These showed that guanethidine produced the same changes in FFA concentration and blood pressure in the two adrenalectomized dogs as in the normal dogs. This indicated that the effect of guanethidine on FFA and blood pressure was not caused by a catecholamine release from the adrenal glands. Athos et al. (3) by direct analysis of the catecholamines in adrenal venous blood were also unable to find any increased secretion of catecholamines after injection of guanethidine.

During a *norepinephrine infusion* the blood pressure rise is mainly due to peripheral vasoconstriction (33). The mechanism of the blood pressure rise caused by guanethidine is not identical as *guanethidine* also markedly stimulates the heart rate and cardiac output (4). It was recently demonstrated that when peripheral vasoconstriction was produced by carotid occlusion and central vagal stimulation, there was no major change in FFA concentration (24). The results suggested that the catecholamines released from the sympathetic vasoconstrictor nerves did *not affect* FFA mobilization. One *could* therefore speculate that guanethidine releases catecholamines not *only* from sympathetic vasoconstrictor

nerves and heart but also from other sources, perhaps from the sympathetic nerves in adipose tissue, which could account for the observed rise in FFA concentration

The effect of different adrenergic blocking agents on the FFA mobilization stimulated by exogenous catecholamines in vivo as well as in vitro has been studied by many authors (1, 15, 20, 22, 29, 30) It was recently reported that phentolamine in doses which completely *inhibited* the blood-pressure rise caused by norepinephrine *did not effectively inhibit* the concomitant rise in FFA concentration (16) In the present investigation it was found that guanethidine also produced a significant rise of FFA concentration in the dogs treated with a dose of phentolamine that completely blocked the blood-pressure rise This suggested that phentolamine was likewise ineffective in inhibiting the FFA mobilization caused by endogenous catecholamines

The FFA mobilization stimulated by exogenous catecholamines, in vivo as well as *in vitro, is inhibited by the administration* of nicotinic acid (7, 8, 16) Nicotinic acid also prevents the FFA mobilization induced by hypoglycemia (17), and that during exercise (*11*) and mental stress (12) Nicotinic acid here inhibited the guanethidine induced rise in FFA concentration If all these facts are considered there seems to be evidence that nicotinic acid also inhibits the FFA mobilization produced by endogenous catecholamines

Summary

The acute effect of guanethidine on the free fatty acids of plasma (FFA) and on *blood pressure has been studied in* anesthetized dogs

After intravenous administration of guanethidine there was a manyfold rise in the plasma FFA concentration The mean blood pressure also increased

Guanethidine produced the same effect on FFA and blood pressure in two adrenalectomized dogs as in the control animals

Pretreatment of dogs with reserpine inhibited the effect of guanethidine on the plasma FFA as well as on the blood pressure

Treatment of dogs with phentolamine inhibited the blood-pressure rise caused by guanethidine, but there was still a significant rise in FFA concentration Nicotinic acid inhibited the FFA concentration rise while the blood pressure rise was unchanged

Acknowledgement

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Heart Rate and Work Load at Maximal Working Intensity in Old Men[1]

By

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It is a wellknown fact that the maximal physical working capacity decreases with rising age in adults For work of 5—10 minutes duration it is generally considered that the working capacity is mainly dependent on the aerobic capacity and can be measured as the maximal oxygen uptake during, for instance, bicycle work From 30 to 60 years of age the mean decline in the total maximal oxygen uptake amounts in men to approximately 25—30 per cent (3 5, 16 22 26 35)

However, it is less known in detail why the physical working capacity decreases with age and what factors limit it in old age The decreased oxygen transporting capacity may either be due to the pulmonary circulatory or muscular and metabolic function or to poor integration of these functions Concerning the circulatory function it is known that the maximal heart rate during exercise in the upright position declines from a mean value of 190—195 beats/min at 20 years of age to around 160—165 beats/min at 60 years of age (3 5 16 26) As also the stroke volume during sitting exercise is lower in old than in young men (14), the maximal cardiac ouput is reduced in old age

The aim of the present investigation was to study in a group of healthy old men the maximal heart rate and work load in different body positions during exercise with varying size of the muscle groups engaged A study was also made of the relationships between maximal heart rate and work load and some parameters of circulatory, pulmonary and metabolic function

Material

In a previous study (30) the selection and examination of 39 healthy males aged 60—83 years was discussed The material in the present study comprised 27 of them *men e g* 12 further subjects were excluded Six *of* these excluded subjects did not participate *owing* to lack of time and interest One subject was excluded because he experienced marked chest pains during the exercise test (never before) one because of a right bundle branch block in the electrocardiogram and one because of ST T depressions at rest

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[1] A preliminary report was given at the annual meeting of the Swedish Medical Society in November 1963

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Table I Some anthropometric data in 27 healthy men aged 61—83 years The symbols are explained under Methods

Case no	Age (yrs)	Height (cm)	Weight (kg)	Physical activity: Earlier	Physical activity: At examination	Total haemoglobin (g)	Blood volume (l)	Heart volume (ml)	W_{170} (kpm/min)	St st$_{\Delta}$ (beats/min)	Log lactate$_{600}$ (log mE/l)	Log lactate$_{900}$ (log mE/l)	Log lactate$_{max}$ (log mE/l)	Electrocardiographic findings during exercise test: 1st test: Total	1st test: ST	1st test: VEB	1st test: SVEB	Repeated tests: ST	Repeated tests: VEB	Repeated tests: SVEB
8	61	187	97	2	2	790	5 64	8ɔɔ	720	19	0 49	0 67	0 87	2	2	1	1	3	1	1
14	62	170	62	1	1	590	4 57	670	3 ı0	4	88	50	88	2	2	1	1	3	1	2
19	64	185	96	2	2	870	6 44	1 070	750	3	—	—	—	5	3	1	1	3	5	1
22	63	178	72	1	2	760	5 71	680	650	4	19	23	62	4	1	1	1	2	1	2
2ɔ	65	172	68	2	2	790	5 34	690	9ɔ0	0	20	50	72	2	2	1	1	2	1	1
28	66	173	83	3	3	790	5 68	850	400	3	49	34	1 03	2	1	1	2	3	1	2
29	65	175	76	2	2	750	5 64	925	760	3	42	59	0 93	3	3	1	1	4	1	1
32	66	170	60	2	2	600	ɔ 17	710	650	11	52	59	94	3	1	3	2	1	3	5
33	68	165	77	3	3	90ɔ	6 33	9ɔ0	490	9	45	43	65	4	1	4	1	1	ɔ	1
34	65	168	81	2	2	795	5 85	1,200	620	8	47	48	78	3	2	1	1	2	1	1
38	68	16ɔ	55	2	2	75ɔ	5 90	875	600	8	61	54	71	5	1	5	1	4	5	5
47	69	182	72	2	2	745	5 9ɔ	970	740	4	15	58	1 00	4	2	4	1	3	5	2
43	67	175	84	3	2	850	6 69	980	ı80	12	40	63	1 02	5	4	4	4	4	5	5
45	69	176	80	3	2	880	6 98	900	650	8	33	41	1 04	4	4	1	1	4	1	ɔ
50	70	176	67	2	1	740	5 83	820	8ɔ0	9	56	81	0 79	5	3	1	5	3	5	5
52	72	177	8ɔ	ɔ	3	990	6 39	1 240	850	16	36	60	7ɔ	5	5	1	2	5	1	5
ɔ4	71	166	63	3	2	615	5 00	800	560	11	64	65	93	2	2	1	1	3	1	2
ɔ6	71	178	91	2	2	880	6 29	805	640	7	56	60	67	ɔ	2	1	5	4	1	5
57	72	1 0	80	2	2	78ɔ	5 34	1 000	760	4	39	46	9ɔ	5	ɔ	1	1	5	5	ɔ
66	73	179	70	2	2	78ɔ	6.28	870	570	9	70	68	88	1	1	1	1	2	3	5
69b	73	172	65	2	1	650	4 71	640	480	18	81	[illegible]	1 02	4	1	4	3	1	5	ɔ
69c	74	172	75	3	1	660	5 79	720	500	8	70	43	0 92	5	3	5	2	5	5	5
70	7ɔ	171	76	2	2	820	6 12	670	690	8	43	57	94	2	2	1	1	3	1	5
7ɔ	80	178	56	2	2	665	5 [illegible]	7ı0	590	6	37	37	53	5	1	5	2	1	5	3
77	81	179	83	2	2	915	6 68	1 070	850	19	50	ı5	63	3	3	1	1	3	5	5
78	81	182	88	3	1	915	7 15	1 415	700	18	83	1 02	1 00	5	1	5	5	1	5	5
ı9	83	163	64	3	2	600	4 96	670	480	10	67	0,50	0 5	4	4	1	2	4	1	2
Mean	ı0	175	7ɔ	2 3	1 9	774	5 84	868	653	8 6	0 50	0 57	0 [illegible]	3 7	2 3	2 ı	1 7	2 9	2 9	3 3
SD	6	5 4	10	0 6	0 5	109	0 67	195	146	5 6	0 19	0 16	0 14	1 3	1 3	1 6	1 2	1 3	2.0	1 8

the last ɔ0—60 seconds of work and analysed according to the Haldane technique More details were given in a previous report (31)

Physical activity

The degree of physical activity at examination and earlier in life was anamnestically estimated and crudely recorded in three classes class one denoting no regular physical training class two a moderate degree of training and class three a high degree of training such as hard bicycling every day cross country running, or hard work e g in the building trade

suggestive of myocardial injury Three subjects were excluded because of pathological ST depressions and ventricular ectopic beats during exercise The electrocardiographic findings in these cases were so marked that the investigator could not possibly be unbiased by them during repeated maximal tests, and these subjects would thus probably not have been stressed as hard as the others

Methods

Heart volume and blood volume

Heart volume was determined by X ray in prone position, and total haemoglobin and blood volume by the alveolar carbon monoxide method These methods were described in previous papers (32, 33)

Lung volumes and ventilatory function

Static lung volumes were determined in sitting position with the helium dilution method using a closed spirometer system (17) Maximal voluntary ventilation was determined with a Bernstein spirometer (Kifa) (10), both at a fixed respiratory rate of 40 beats/min and at a free rate Forced vital capacity tests were also performed with this spirometer The mean values in the present study did not differ from previous reported values in this country (15)

Oscillography

For determination of the arterial pulsations in the lower legs oscillograms were recorded with the oscillograph of Gesenius and Keller (Bosch & Speidel, Jungingen Hohenzollern, W Germany) in 18 subjects at rest in supine position The cuff was placed 8 cm below the knee joint

Exercise tests

The subjects exercised on an electrodynamically braked bicycle ergometer both in sitting and supine positions The test started at a load of 300 kpm/min which was increased every sixth minute by a further 300 kpm/min until the subjects were exhausted It was intended that maximal values should be reached in all tests The work load at maximal working intensity (W_{max}) was taken to be the heaviest load at which the subject worked for 6 minutes with an increment proportional to the completed part of the period at the next higher load Heart rate was determined from electrocardiographic recordings of at least 10 beats, generally 25 During the last minutes of the test the recordings were continuous. HR_{max} was taken to be the highest heart rate value that was recorded during exercise All subjects performed at least one test in supine (except case nr 19) and at least two in sitting position Twelve subjects performed more than two tests in sitting position A more detailed description of the testing procedure has been given in previous reports (30, 31)

Most of the subjects also performed one test in sitting position with leg work combined with arm work Another bicycle ergometer with handles instead of pedals was then arranged on the leg bicycle in the position of the handle bar, and the subjects cranked with the arms simultaneously with the leg work An advantage of the bicycles used was that their work loads in kpm/min were kept constant within a rather wide range of pedalling rate (18) so the arms and legs could work at different and varying rates The subjects trained on the technique once or twice on separate days before the test and then chose the relationships between arm load and leg load For a subject completing 900 kpm/min in the sitting test with only leg work, the combined test usually started at 300 and 600 kpm/min with the legs, followed by 700 kpm/min with the legs and 200 kpm/min with the arms, and then increasing to 900 and 300 kpm/min respectively

The determination of the working intensity at heart rate 130 (W_{130}), 2—6 min heart rate increase at heart rate 130 (St st_{130}), log arterial lactate at 600 kpm/min (log $lact_{600}$) and at heart rate 130 (log $lact_{130}$) have been described in detail earlier (31, 32 33) Log arterial lactate at maximal working intensity (log $lact_{max}$) was either measured during or immediately after exercise or estimated by a short extrapolation from submaximal up to maximal heart rates

The recording and assessment of the electrocardiographic findings during the exercise tests have been discussed earlier (30) The ST interval the ventricular ectopic beats and the supraventricular ectopic beats were independently classified in five classes class one being regarded as normal and class five as abnormal

Oxygen uptake at maximal working intensity was determined by the Douglas bag technique, expired air being collected during

Table III Subjective complaints at interruption of test under different conditions

	No of subjects	Dyspnoea		Fatigue in the muscles		General tiredness	
		Most marked complaint	Secondary or most marked complaint	Most marked complaint	Secondary or most marked complaint	Most marked complaint	Secondary or most marked complaint
Sitting position	26	12	12	9	11	5	10
Supine position	25	9	16	16	21	–	4
Arm + leg work	17	9	13	6	8	2	6

Statistical calculations

These were made according to Snedecor (28) when not otherwise stated The following probality (P) levels of significance were used $P < 0.001$*** highly significant $P < 0.01$** significant and $P < 0.05$* probably significant Multiple regression analyses were performed by the method of least squares The method employed was discussed in greater detail in a previous study (32)

Results

Individual and mean values for some anthropometric data are given in table I

Subjective complaints at break of test

The subjective complaints on interruption of the test are given in table II and table III Case no 79 was objectively hard stressed but could not explain why he stopped The incidence of fatigue in the legs as most marked complaint was slightly higher during exercise in supine than in sitting position (table III) but the difference was not significant (chi square = 3 3 $0.1 > P > 0.05$) Including fatigue in the legs as a secondary complaint the difference between supine and sitting position was significant (chi square = 7 8**) Using the tables for fourfold contingency tests of Mainland and Murray (25) which are more exact in small samples the difference was of probable significance ($0.02 > P > 0.01$) Apart from the complaints listed in table II case nos 33, 45 and 52 reported a slight feeling of pressure in the chest in supine position There was no difference of probable significance between the complaints during sitting leg work and sitting leg work combined with arm work

Heart rate, work load and arterial lactate concentration at maximal working intensity

Individual and mean values for heart rate and work load at maximal working intensity (HR_{max} and W_{max}) under different conditions are given in table II The mean age in the 60—69 year group was 65 5 years, in the 70—75 year group 72 3 years and in the 80—83-year group 81 3 years

Sitting position The mean HR_{max} in sitting position (table II) decreased with age from 166 5 beats/min in the 60—69-year group to 155 0 and 139 5 beats/min in the 70—75 and 80—83 year groups The mean W_{max} decreased similarly with age from 928 kpm/min to 818 and 650 kpm/min

The mean individual difference in HR_{max} between the first test and the one of the other tests in sitting position with the highest HR_{max} was only — 3 beats/min and not of significance (table IV)

Table II Subjective complaints, heart rate (HR_{max}) and work load (W_{max}) and oxygen uptake ($\dot{V}_{O_2max}$) at maximal working intensity under different conditions in 27 men aged 61—83 years

Case no	Subjective complaints			HR_{max} (beats/min)				W_{max} (kpm/min)				$\dot{V}_{O_2max}$ (l/min) sitt
	1st test sitt	Sup	Arm + leg	1st test sitt	Sitt	Sup	Arm + leg	1st test sitt	Sitt	Sup	Arm + leg	
8	b	b	b	136	153	131	165	775	810	700	1 040	2.34
14	c	b+a		180	180	163	—	600	600	400	—	1.57
19	b			158	167	—	—	950	975	—	—	
22	a+c	b+a	c	168	168	153	176	1 000	1 000	665	975	
25	a	b+c	b	146	146	128	148	1,150	1 150	875	1 200	2.44
28	a+c	a+b	a	192	192	170	195	1,100	1,100	900	1,225	2.79
29	b	b+a	b+a	146	171	158	168	900	1,100	750	1,000	
32	c	b+a	c+a	162	164	128	163	800	900	600	955	1.94
33	a	a+b		152	159	148	—	700	750	650	—	2.19
34	b	b+c		163	167	128	—	800	850	600	—	
38	b	b	d	152	152	129	156	700	700	600	650	
42	a+c	b+a		160	160	142	—	1,100	1,100	950	—	2.64
43	a	a+c	a+c+d	168	169	156	168	825	1,000	800	1,100	2.22
45	b	a+b	a+c	164	183	150	175	900	950	725	1,000	
50	b	b	a	118	126	117	134	675	675	625	700	1.58
52	a+c	a		144	144	116	—	950	950	700	—	2.06
54	c	b	b+c	166	168	148	166	900	900	725	900	2.10
56	a	a+c	a+d	158	158	151	160	900	900	740	900	2.28
57	a	a+b	a+b+d	158	161	158	162	940	950	900	1,100	
66	b+c	a	a+b	141	160	144	162	625	675	500	675	
69b	a	a+b	a	166	166	151	162	660	660	610	700	1.70
69c	a+b	b	a+c	155	156	130	160	710	750	610	850	2.14
70	a+b	b+a		154	156	138	—	900	900	690	—	2.04
75	c	b		153	159	131	—	735	735	600	—	1.47
77	c	b	b+a	126	126	110	144	650	650	550	625	1.25
78	b	b+a	b+a	117	128	121	138	600	600	600	650	1.75
79	?	?	?	140	145	118	160	550	615	400	600	1.52
Age group (yrs)	61—69	Mean		160.5	166.5	144.9	168.2	879	928	709	1 017	2.27
		SD		14.4	12.6	14.9	13.3	166	167	150	167	0.39
		n		14	14	13	9	14	14	13	9	8
	70—75	Mean		151.1	155.0	139.2	158.0	807	818	678	832	1.99
		SD		15.0	12.9	15.2	10.8	135	125	112	153	0.25
		n		9	9	9	7	9	9	9	7	7
	80—83	Mean		134.0	139.5	120.0	147.3	634	650	538	625	1.50
		SD		15.8	15.5	8.7	11.4	79	60	95	25	0.21
		n		4	4	4	3	4	4	4	3	4
	61—83	Mean		153.4	158.7	139.1	161.2	818	850	672	887	2.00
		SD		17.0	15.9	16.3	13.9	166	170	139	204	0.42
		n		27	27	26	19	27	27	26	19	19

Sitt = *sitting position* Sup = supine position Arm + leg = combined arm work and leg work
a = dyspnoea b = fatigue in the working muscles, c = general fatigue d = coordination trouble

Table III Subjective complaints at interruption of test under different conditions

	No of subjects	Dyspnoea		Fatigue in the muscles		General tiredness	
		Most marked complaint	Secondary or most marked complaint	Most marked complaint	Secondary or most marked complaint	Most marked complaint	Secondary or most marked complaint
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Supine position	25	9	16	16	21	—	4
Arm + leg work	17	9	13	6	8	2	6

Statistical calculations

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Results

Individual and mean values for some anthropometric data are given in table I

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The subjective complaints on interruption of the test are given in table II and table III Case no 79 was objectively hard stressed but could not explain why he stopped The incidence of fatigue in the legs as most marked complaint was slightly higher during exercise in supine than in sitting position (table III) but the difference was not significant (chi square = 3 3, $0.1 > P > 0.05$) Including fatigue in the legs as a secondary complaint the difference between supine and sitting position was significant (chi square = 7 8**) Using the tables for fourfold contingency tests of Mainland and Murray (25) which are more exact in small samples the difference was of probable significance ($0.02 > P > 0.01$) Apart from the complaints listed in table II, case nos 33, 45 and 52 reported a slight feeling of pressure in the chest in supine position There was no difference of probable significance between the complaints during sitting leg work and sitting leg work combined with arm work

Heart rate, work load and arterial lactate concentration at maximal working intensity

Individual and mean values for heart rate and work load at maximal working intensity (HR_{max} and W_{max}) under different conditions are given in table II The mean age in the 60—69 year group was 65 5 years, in the 70—75 year group 72 3 years and in the 80—83 year group 81 3 years

Sitting position The mean HR_{max} in sitting position (table II) decreased with age from 166 5 beats/min in the 60—69 year group to 155 0 and 139 5 beats/min in the 70—75 and 80—83 year groups The mean W_{max} decreased similarly with age from 928 kpm/min to 818 and 650 kpm/min

The mean individual difference in HR_{max} between the first test and the one of the other tests in sitting position with the highest HR_{max} was only — 3 beats/min and not of significance (table IV)

Table IV Mean individual differences in heart rate and work load at maximal working intensity under different conditions in 27 men aged 61—83 years

	1st test sitting — — other tests sitting	Supine test — — best sitting test	Supine test — — preceding sitting test	Arm—leg test— — best sitting test	Arm—leg test— — preceding sitting test
No of subjects	27	26	26	19	19
	Heart rate (beats/min)				
Mean	−3 0	−19.2	−14 4	3 7	6 6
SD	9 6	9 1	10.9	6.7	8.7
P	>0 1	***	***	*	**
	Work load (kpm/min)				
Mean	−5	−174	−145	40	63
SD	82	90	89	77	89
P	>0 7	***	***	*	**

P = probability that the differences are caused by random factors (see Methods)

The corresponding mean difference in W_{max} was also insignificant It was thus possible in this material to reach "maximal" heart rates and work loads in the first exercise test

The mean lactate concentration at maximal working intensity in sitting position was 7 2 mE/l (0 86 ± 0 14, mean ± SD, log mE/l, table I) There was no correlation of probable significance between age and log $lact_{max}$ (r = —0 14)

Supine position The mean HR_{max} in supine position (table II) decreased with age from 145 beats min in the 60—69-year group to 139 and 120 beats min in the 70—75-and 80—83-year group The mean W_{max} decreased similarly with age from 709 kpm/min to 678 and 538 kpm/min

In supine position HR_{max} was significantly lower than in sitting position, the mean difference was 19 beats min (table IV) Compared to the preceding test in sitting position the mean difference was 14 beats/min With the same significance the mean W_{max} was 174 kpm min or 20 6 % lower in supine than in sitting position Compared to the preceding test in sitting position the mean difference was 145 kpm/min or 17 1 %

The mean lactate concentration in supine position at maximal working intensity was 5 7 mE/l (n = 21) The mean individual difference between log $lact_{max}$ in sitting and supine position was highly significant and amounted to 0 099 ± 0 083 (mean ± SD) log mE/l (n = 21) The mean value was thus 1 4 mE l or 20 % lower in supine position The correlation coefficient between log $lact_{max}$ in supine and sitting position was 0 84***

Combined arm work and leg work The mean HR_{max} for combined arm work and leg work (table II) decreased with age from 168 beats min in the 60—69-year group to 158 and 147 beats/min in the 70—75 and 80—83-year groups The mean W_{max} decreased similarly with age from 1,017 kpm min to 832 and 625 kpm min

In combined arm work and leg work HR_{max} was slightly higher than the highest value during exercise with the

legs only, the mean difference of 3 7 beats/min was of probable significance (table IV) Compared to the preceding test in sitting position the mean difference of 6 6 beats/min was significant With the same significance the mean W_{max} was 40 kpm/min or 5 % higher than during leg work Compared to the preceding test with leg work the mean difference in W_{max} was 63 kpm/min or 7 %

The mean lactate concentration at maximal working intensity during combined arm and leg work was 7 7 mE/l (n = 16) The mean individual difference between log $lact_{max}$ during leg work and during combined arm work and leg work was 0 005 ± 0 146 (mean ± SD) log mE/l *i e* not of probable significance

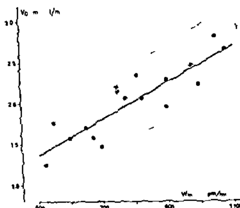


Fig 1 Oxygen uptake (y V_{O_2max}) in relation to work load (x W_{max}) at maximal working intensity during sitting exercise in 19 men aged 61—83 years Regression line and 95 per cent confidence belts for single observations Regression equation y = 0.262 + 0 00219x, r = 0 88*** SD = 0 203 n = 19

Oxygen uptake at maximal working intensity

In 19 of the subjects at least one of the tests in sitting position included determination of oxygen uptake at maximal working intensity (V_{O_2max} table II) The mean V_{O_2max} decreased with age from 2 27 l/min in the 60—69 year group to 1 99 and 1 50 l/min in the 70—75 and 80—83 year groups The regression equation for V_{O_2max} (y l/min) on age (x years) was y = 4 72 — 0 038x (SD — ± 0 35 l/min r = 0 59** n = 19), *e g* for 10 years increase in age V_{O_2max} decreased 0 38 l/min

The relationship between V_{O_2max} and W_{max} is given in fig 1 It is to be noted that the mean values for oxygen uptake during submaximal work loads in old men in previous studies (3 31) almost exactly correspond to the present regression line for V_{O_2max} on W_{max} The standard deviation for prediction of V_{O_2max} from W_{max} (± 0 20 l/min or ± 10 1 % of the mean value) was approximately twice the values given for the standard deviation of oxygen uptake at submaximal work loads

Statistical analyses

HR_{max} as dependent variable Some of the relationships that were obtained with HR_{max} as dependent variable in regression and multiple regression analysis are given in table V For none of the independent variables in table V and VI was the relationship with age of probable significance Both parameters recorded at rest at submaximal and at maximal working intensities were used as independent variables Regressions including parameters recorded at maximal working intensity are of course, of little practical value for predicting HR_{max} or W_{max} but may be of theoretical interest.

The lowest residual standard deviation was obtained with log arterial lactate concentration at heart rate 130 (log

Table V Heart rate (y, HR_{max}, beats/min) at maximal working intensity in relation to log arterial lactate at heart rate 130 (log $lact_{130}$, log mE/l), age (yrs), W_{130} (kpm/min), 2—6 min heart rate increase at heart rate 130 ($St\ st_{130}$ beats/min), heart rate in standing position (HR_{st}, beats/min), log arterial lactate at maximal working intensity (log $lact_{max}$, log mE/l) and anamnestic degree of physical activity (phys act, scale 1—3) in 26 healthy men aged 61—83 years The section number indicates the number of independent variables Mean value ± SD for HR_{max} = 158.5 ± 15.8 or ± 10.0 % of the mean r = correlation coefficient, R = multiple correlation coefficient

Section	Independent variable	Regression equation	Residual SD beats/min	Residual SD % of mean	b/εb	r	R
1	Log $lact_{130}$	$y = 192 - 59x$	13.1	8.2	−3.54**	−0.586	
	Age	$y = 261 - 1.46x$	13.5	8.5	−3.23**	−0.551	
	W_{130}	$y = 197 - 0.059x$	13.5	8.5	−3.23**	−0.550	
	$St\ st_{130}$	$y = 171 - 1.43x$	14.1	8.9	−2.67*	−0.479	
	HR_{st}	$y = 113 + 0.58x$	14.2	8.9	2.66*	0.477	
2	Age (x_1)	$y = 298 - 1.44x_1 - 0.058x_2$	10.4	6.6	−4.13***		0.774
	W_{130} (x_2)				−4.12***		
	W_{130} (x_1)	$y = 213 - 0.044x_1 - 47x_2$	11.7	7.4	−2.64*		0.705
	Log $lact_{130}$ (x_2)				−2.98**		
	Age (x_1)	$y = 259 - 1.06x_1 - 46x_2$	11.8	7.4	−2.52*		0.697
	Log $lact_{130}$ (x_2)				−2.86**		
	W_{130} (x_1)	$y = 205 - 0.054x_1 - 1.27x_2$	11.9	7.5	−3.34**		0.694
	$St\ st_{130}$ (x_2)				−2.82**		
	Age (x_1)	$y = 213 - 1.34x_1 + 0.51x_2$	11.9	7.5	−3.34**		0.693
	HR_{st} (x_2)				2.80*		
3	Age (x_1)	$y = 290 - 1.18x_1 - 0.048x_2 - 30x_3$	9.7	6.1	−3.42**		0.819
	W_{130} (x_2)				−3.53**		
	Log $lact_{130}$ (x_3)				−2.20*		
	Age (x_1)	$y = 263 - 1.35x_1 - 0.054x_2 + 30x_3$	9.7	6.1	−4.11***		0.817
	W_{130} (x_2)				−4.06***		
	Log $lact_{max}$ (x_3)				2.14*		
4	Age (x_1)	$y = 244 - 1.05x_1 - 0.050x_2 + 34x_3 - 0.90x_4$	8.7	5.5	−3.28**		0.863
	W_{130} (x_2)				−4.16***		
	Log $lact_{max}$ (x_3)				2.67*		
	$St\ st_{130}$ (x_4)				−2.50*		
5	Age (x_1)	$y = 214 - 0.93x_1 - 0.051x_2 + 42x_3 - 0.83x_4 + 7.7x_5$	7.7	4.9	−3.25**		0.900
	W_{130} (x_2)				−4.84***		
	Log $lact_{max}$ (x_3)				3.62**		
	$St\ st_{130}$ (x_4)				−2.62*		
	Phys act (x_5)				2.64*		

$lact_{130}$) as the independent variable, followed by age intensity of work at heart rate 130 (W_{130}), 2—6 min heart rate increase at heart rate 130 (St st_{130}) and heart rate in standing position (HR_{st}) (section 1 table V) Except for HR_{st} all the correlations were negative A low HR_{max} was thus connected with a high age a high value for lactate concentration at heart rate 130 and lack of heart rate steady state (high St st_{130}) at heart rate 130 A low HR_{max} was also connected with a low heart rate at rest, both supine (see below) and standing and a low heart rate during exercise (high W_{130}) According to the regression on age an increase in age of 10 years corresponded to a decrease in HR_{max} of 14 2 beats/min Besides the correlations listed in table V, HR_{max} was also correlated to heart rate at 600 kpm/min ($r = 0\ 54^{**}$) W_{max} 0 42*), log $lact_{max}$ (0 41*) and heart rate at rest supine (0 41*)

Body weight height heart volume total haemoglobin haemoglobin concentration and blood volume were not of probable significance when tested alone or in combination with any of the other independent variables Nor were any of the assessments of the electrocardiographic findings of probable significance As parameters of lung volumes and ventilatory function the total lung capacity (TLC) vital capacity functional residual capacity (FRC) residual volume (RV), FRC TLC RV/TLC forced vital capacity FVC) FVC_{1}, FEV %, maximal voluntary ventilation and respiratory rate at 600 kpm min were tested as independent variables However none of them was of probable significance when tested alone or in combination with the variables in table V

When the regression computations were performed with two independent variables (section 2, table V) the lowest residual standard deviations were obtained with age and W_{130} followed by W_{130} and log $lact_{130}$ age and log $lact_{130}$, W_{130} and St st_{130}, and age combined with HR_{st}

In combination with other variables W_{130} gave slightly lower residual standard deviations than heart rate at 600 kpm/min W_{max} lost its probable significance when tested together with age as did HR_{st} and heart rate at rest supine when they were combined with W_{130}

With three independent variables (section 3, table V) the lowest residual standard deviations were obtained with age, W_{130} and log $lact_{130}$ and with age, W_{130} and log $lact_{max}$ A low HR_{max} was thus connected with a low value for log $lact_{max}$ The best combination of four variables was a combination of age, W_{130} log $lact_{max}$ and St st_{130} (section 4, table V)

The only variable studied that was of probable significance together with age, W_{130} log $lact_{max}$ and St st_{130} was the anamnestic degree of physical activity at the time of the examination (phys act section 5 table V) A low HR_{max} was then connected with a low degree of physical activity The physical activity, however, was not of probable significance as single variable ($r = 0\ 24$), nor in combination with age with W_{130}, with St st_{130} or with log $lact_{max}$

With these five variables the residual standard deviation decreased to $\pm 7\ 7$ beats/min or $\pm 4\ 9$ % of the mean HR_{max}, compared to the original standard deviation of $\pm 15\ 8$ beats/min or $\pm$ 10 0 %

W_{max} *as dependent variable* Some of the relationships that were obtained with W_{max} as dependent variable in regression and multiple regression analysis are given in table VI

Table VI Work load (y, W_{max}, kpm/min) at maximal working intensity in relation to some parameters in 26 healthy men aged 61—83 years Log $lact_{600}$ = log arterial lactate concentration at 600 kpm/min St st_{600} = 2—6 min heart rate increase at 600 kpm/min Other symbols as in table I Mean value ± SD or W_{max} = 847 ± 170 kpm/min or ± 20.1 % of the mean

Section	Independent variable	Regression equation	Residual SD kpm/min	Residual SD % of mean	b/ε_b	r	R
1	Log $lact_{600}$	$y=1{,}195-692x$	110	13.0	−6.04***	−0.776	
	St st_{600}	$y=984-17.1x$	143	16.9	−3.41**	−0.571	
	St st_{130}	$y=1{,}001-16.9x$	148	17.5	−3.04**	−0.527	
	Age	$y=1\,846-14.2x$	151	17.8	−2.80**	−0.495	
	Phys act	$y=563+148x$	152	17.9	2.72*	0.485	
	HR_{max}	$y=126+4.55x$	158	18.6	2.28*	0.422	
	W_{130}	$y=550+0.458x$	159	18.8	2.13*	0.399	
	Log $lact_{130}$	$y=1{,}090-427x$	160	18.9	−2.09*	−0.392	
2	Log $lact_{600}$ (x_1)	$y=591-659x_1+3.70x_2$	94	11.1	−6.64***		0.848
	HR_{max} (x_2)				3.09**		
	Log $lact_{600}$ (x_1)	$y=1\,757-615x_1-8.52x_2$	100	11.8	−5.64***		0.827
	Age (x_2)				−2.44*		
	St st_{600} (x_1)	$y=1\,793-15.0x_1-11.73x_2$	127	15.0	−3.32**		0.700
	Age (x_2)				−2.71*		
	St st_{130} (x_1)	$y=672-18.5x_1+0.529x_2$	127	15.0	−3.83***		0.698
	W_{130} (x_2)				3.05**		
3	St st_{130} (x_1)	$y=460-16.6x_1+0.489x_2+115x_3$	111	13.1	−3.88***		0.792
	W_{130} (x_2)				3.22**		
	Phys act (x_3)				2.86**		
	St st_{130} (x_1)	$y=284-19.3x_1+0.591x_2+416x_3$	115	13.5	−4.41***		0.775
	W_{130} (x_2)				3.75**		
	Log $lact_{max}$ (x_3)				2.50*		
4	St st_{130} (x_1)	$y=-124-17.0x_1+0.559x_2+$ $+149x_3+559x_4$	79	9.3	−5.60***		0.905
	W_{130} (x_2)				5.14***		
	Phys act (x_3)				5.03***		
	Log $lact_{max}$ (x_4)				4.74***		
	St st_{130} (x_1)	$y=1\,046-13.3x_1+0.482x_2+$ $+106x_3-8.44x_4$	102	12.0	−3.18**		0.837
	W_{130} (x_2)				3.48**		
	Phys act (x_3)				2.84*		
	Age (x_4)				−2.28*		
5	St st_{130} (x_1)	$y=338-14.7x_1+0.549x_2+$ $+139x_3+509x_4-5.90x_5$	73	8.6	−4.90***		0.924
	W_{130} (x_2)				5.48***		
	Phys act (x_3)				5.05***		
	Log $lact_{max}$ (x_4)				4.59***		
	Age (x_5)				−2.18*		

The lowest residual standard deviation was obtained with log arterial lactate concentration at 600 kpm/min (log $lact_{600}$) as the independent variable, followed by 2—6 min heart rate increase at 600 kpm/min (St st_{600}), St st_{130} age, anamnestic degree of physical activity, HR_{max}, W_{130} and log $lact_{130}$ (section 1, table VI) The sign of the regression coefficients indicated that a low W_{max} was connected with a high age, high values for lactate concentration and lack of heart rate steady state (high St st_{600} and St st_{130}) during exercise A low W_{max} was also connected with a low degree of physical activity and with low values for W_{130} and HR_{max} According to the regression on age an increase in age of 10 years corresponded to a decrease in W_{max} of 142 kpm/min

As for HR_{max} the body weight, height, heart volume total haemoglobin, haemoglobin concentration blood volume, assessments of the electrocardiographic findings and the studied parameters of lung volumes and ventilatory function, were not even of probable significance when tested alone or in combination with any of the significant independent variables

With two independent variables (section 2 table VI) the lowest residual standard deviations were obtained with log $lact_{600}$ and HR_{m} followed by log $lact_{600}$ and age St st_{600} and age and St st_{130} combined with W_{130} When age and HR_{max} were tested together, none of the variables were of probable significance

When the regression computations were performed with three independent variables it was noted that none of the studied variables were of probable significance when tested together with log $lact_{600}$ and HR_{max} or log $lact_{600}$ and age No further reduction of the residual standard deviation could be obtained with three independent variables when log $lact_{600}$ was excluded (section 3, table VI) However, by substituting log $lact_{600}$ by three other variables obtained at rest or during submaximal exercise (section 4, table VI) similar residual standard deviations were recorded The lowest residual standard deviation was obtained by substituting log $lact_{600}$ by four, and using altogether five, independent variables (section 5, table VI)

With five independent variables the residual standard deviation decreased to $\pm$ 73 kpm/min or $\pm$ 8 6 % of the mean W_{max} compared to the original standard deviation of $\pm$ 170 kpm/min or $\pm$ 20 1 % These five independent variables were the same as for HR_{max} Neither log $lact_{max}$ nor the anamnestic degree of physical activity were of probable significance when tested alone A low W_{max} was connected with poor heart rate steady state during exercise (high St st_{130}), high heart rate during exercise (low W_{130}), low degree of physical activity, low values for arterial lactate concentration at maximal working intensity and a high age These relationships were the same as for HR_{max} except that a high W_{130} corresponded to a high W_{max} but to a low HR_{max}

Correlation between arterial calf pulsations and W_{max} In 18 of the subjects the arterial pulsations at rest were recorded in the calves by oscillography The mean value for the 36 legs was 10 5 mm with a standard deviation of $\pm$ 2 6 mm This value is in accordance with earlier reports (20) The highest quotient between the amplitudes of the right and left or left and right sides was 1 5 (17/11) The lowest amplitude (5 mm in both legs) was recorded in the oldest subject case number 79

Table VII Total and some partial correlation coefficients (r) between W_{max} (1), arterial calf pulsations (2), log $lact_{600}$ (3) and age (4) in 18 healthy men aged 61—83 years

Total r	Partial r
$r_{12} = +0.47$*	$r_{12 \cdot 3} = +0.59$*
$r_{13} = -0.69$**	$r_{12 \cdot 4} = +0.23$
$r_{14} = -0.60$**	$r_{12 \cdot 34} = +0.48$
$r_{23} = -0.07$	$r_{13 \cdot 4} = -0.67$**
$r_{24} = -0.53$*	$r_{14 \cdot 3} = -0.11$
$r_{34} = +0.49$	$r_{23 \cdot 14} = +0.49$
	$r_{24 \cdot 13} = -0.45$

The total and some partial correlation coefficients between W_{max} in sitting position, the individual mean arterial calf pulsations at rest, log $lact_{600}$ and age are given in table VII There was a probably significant correlation between W_{max} and the arterial pulsations, which was lost, however, when the influence of age or of log $lact_{600}$ and age was eliminated The arterial pulsations were not correlated to log $lact_{600}$ but showed a probably significant correlation to age This slight correlation to age was also lost, however, when the influence of W_{max} and log $lact_{600}$ was eliminated Slightly lower correlation coefficients were obtained when W_{max} in supine position was used instead of W_{max} in sitting position and when the lowest value of the individual calf pulsations at rest was used instead of the individual mean value

Discussion

Subjective complaints at break of test and arterial calf pulsations at rest

The finding of dyspnoea as the most frequent complaint on interruption of the exercise test in the age group studied was discussed in a previous paper (31) The higher incidence of fatigue in the legs during supine compared to sitting exercise might be attributed to a higher degree of anaerobic metabolism in the working muscles in this position Higher levels of arterial lactate concentration during supine compared to sitting exercise were thus found in these men in a previous study (31) During supine exercise the elevation of the limbs causes a hydrostatic counterpressure in the arterial system of the limbs A special work test in supine position with elevated legs has been devised in order to evaluate the peripheral arterial circulation in obstructive arterial disease (24) Other factors which might be more important for the difference between supine and sitting position than the hydrostatic counterpressure are discussed below

In patients with intermittent claudication the reduction of the calf pulsations at rest was related to the reduction in maximal calf blood flow immediately after exercise and the work load at maximal working intensity (34) In the present material there was a slight positive correlation between calf pulsations and W_{max} which, however, was lost after eliminating the effect of age Nor was there any correlation of probable significance between the calf pulsations and the arterial lactate concentration during exercise It is therefore not probable that the decline in W_{max} with age in this material was related to obstructive changes in the main arteries of the legs

W_{max} in relation to $\dot{V}_{O_2 max}$

When determining the individual value of W_{max} every minute of work at the highest load was counted equal Concerning the aerobic capacity, however, the ability to work the first two minutes at the load should increase the oxygen uptake more than the ability to continue

the exercise from the fourth to the sixth minute (8) This difference will of course increa e the random error in prediction of V_{O_2max} but should not cause significant ystematic errors in a large material In the present study the regression of V_{O_2max} on W_{max} was the same as for oxygen uptake on work load during submaximal exercise This should be in accordance with the previous observation that oxygen uptake was not related to the arterial lactate concentration at the work load (31) and suggests that W_{max} did not include a significant anaerobic component but was related to the aerobic capacity

HR_{max} W_{max} and V_{O_2max}

Effect of age and body position The values observed in the present study for HR_{max} and V_{O_2max} in the different age groups are similar or slightly higher than previous reported values in sitting or standing position (3 16, 26, 35) as are the values in supine position (22, 23) The lower values for HR_{max} and W_{max} in supine compared to sitting exercise are also in accordande with the findings in young and well trained subjects (9) Besides the effect of the hydrostatic counterpressure discussed above the difference between supine and sitting position may be attributed to the possibility that smaller muscle groups or less well trained muscle groups are engaged in supine position Thi possibility should be in agreement with the observed higher values for arterial lactate concentration during su pine exercise in these men (31) as it is known that exercise with the smaller muscle groups in the arms will give higher blood lactate levels during exercise and lower values for maximal oxygen uptake than exercise with the larger muscle groups in the legs (1 2 9, 11)

Effect of combined arm work and leg work No significant differences concerning the cardiac output in relation to oxygen uptake were observed between submaxi mal leg work and leg work in combination with arm work in young men (11) As the oxygen uptake is higher in relation to work load during arm work of this type than during leg work (12) the higher W_{max} and HR_{max} during combined arm work and leg work in the present study most probably corresponded to a higher cardiac output at maximal working intensity than during only leg work in sitting position This might be interpreted as a sign that the engagement of larger muscle masses in the combined arm and leg work was necessary for the increase in heart rate and work load However, the main rea on does not seem to be the larger muscle masses engaged, but the effect of counterirritation i e the afferent inflow from the arms or the mental concentration on cranking with the arms eemed to suppress the afferent inflow from the legs For it was observed in the present study that at constant working intensity with the legs, close to the maximal value, an immediate decrease of the feeling of exhaustion was experienced when arm work starts as well The effect starts within a few seconds and appears to be too rapid to be associated with possible changes in lactate elimina tion and production

HR_{max} as dependent variable

The mo t significant parameter for prediction of HR_{max} in the present material was log arterial lactate con centration at heart rate 130, which is a relative measurement of the degree of anaerobic metabolism during exercise However, in combination with other parameters, age and W_{130} were more significant for this prediction

The regression coefficient for HR_{max} on age decreased approximately by one-third after eliminating the effects of four other independent variables, which indicates that this part of the decline of HR_{max} with age was better taken into account by the interindividual variations of these parameters The way in which age influences HR_{max} cannot be evaluated at present

A low HR_{max} was related both to a low heart rate at rest and to a low heart rate during exercise (high W_{130}), but the best correlation was with W_{130} W_{130} provides an estimate of the oxygen pulse during exercise at that heart rate and, as such, is a measure of the cardiovascular function

The third significant independent variable was log arterial lactate concentration at maximal working intensity This parameter will probably account mostly for variations in the willingnesss of the subjects for physical exhaustion i e in their sensitivity to anaerobic metabolism during exercise, but other factors may also be involved

It might be expected that low values of HR_{max} would be connected with a general inertia of the heart rate reaction during exercise On the contrary, the subjects with low 2—6 min heart rate increases at heart rate 130 (St st_{130}) achieved higher HR_{max} than those who were not in a relative heart rate steady state The importance of taking the heart rate steady state into account when estimating the physical working capacity has been stressed repeatedly (27) The close correlation between heart rate steady state and arterial lactate concentration has been pointed out earlier (31) In the present material the total correlation coefficient between St st_{130} and Log $lact_{130}$ was 0 62***, and the partial correlation coefficient after eliminating the effect of age was 0 57**

The fifth independent variable of probable significance was the anamnestic degree of physical activity It is well known that physical training increases the maximal cardiopulmonary function It also increases the ability to perform submaximal work without signs of anaerobic metabolism, i e without marked increase of the blood lactate (19) It is probable that this muscular or muscular metabolic factor is taken into account by the anamnestic degree of physical activity in the present study

W_{max} as dependent variable

As for HR_{max} there was no correlation of even probable significance between W_{max} and body weight height, heart volume, blood volume or total haemoglobin This is contrary to the findings in younger subjects, whose W_{170} as a measure of physical working capacity was found to be closely related both to heart volume and total haemoglobin (21), and in young girl swimmers in whom there was a highly significant regression of maximal oxygen uptake on heart volume also when total haemoglobin was included as independent variable (7) A probably significant correlation between heart volume at rest and maximal oxygen uptake during steady state supine exercise was also observed in a material of 60—75 year old males (23) The findings in the present material that the maximal working intensity was not related to the dimensions of the cardiovascular system, should suggest that other factors were more important for this function

The best correlation was the negative one between W_{max} and log arterial lactate concentration at 600 kpm min In a previous study of lactate and pyruvate

during exercise in some of these men (31) it was shown that during these exercise tests, the values for excess lactate simply corresponded to the values for lactate reduced by 2 mM/l The lactate values in the present study should then be expected to reflect the anaerobic metabolism in the working muscles and the data suggest that this should be the main limiting factor for the maximal working capacity in the present material It is probably related to peripheral factors as has been suggested before (6 13), and may be related to the muscular mass engaged in the exercise to distribution of muscle blood flow, to diffusion of oxygen from the capillaries into the muscle cells, and to metabolic cellular factors

The influence of age, W_{130}, log $lact_{max}$, St st_{130} and anamnestic degree of physical activity on W_{max} was mainly the same as discussed in connection with HR_{max} It should be noted, however, that a high W_{130} corresponded to a high W_{max} but to a low HR_{max} The value of W_{130} as an estimate of the oxygen pulse during exercise was then positively and highly significantly related to the maximal performance of the subject, despite the negative correlation with the maximal heart rate

The present findings, that the assessment of the ECG was without significance for HR_{max} is in agreement with earlier reports (4 30) In the present study, however three subjects were excluded because of marked electrocardiographic changes during the first exercise test These three subjects had similar HR_{max} to the others, but somewhat lower W_{max} (mean 625 kpm/min range 500—700) Including these three subjects the correlation between W_{max} and the assessment of ventricular ectopic beats was of probable significance (r = —0 41*), but after elimination of the effect of age it was not (—0 36)

The lack of correlation between W_{max} or HR_{max} and lung volumes or measurements of pulmonary ventilatory function should indicate that ventilatory factors did not significantly limit the capacity for this type of physical exercise in the present material of old males Of course this does not exclude the possibility of pulmonary limitation in some of the subjects Besides a slight effect of pulmonary limitation may already have been taken into account in the other significant independent variables In the present study however there was no correlation of probable significance between the pulmonary parameters and any of the significant or probably significant independent variables Nor were signs of pulmonary insufficiency present during maximal working intensity when arterial oxygen and carbon dioxide tensions were studied in some of these men (29)

Exercise test for old men

Judging from the present and previous (32, 33) findings in this material of old men the following suggestions for exercise tests for old men may be given

When the primary interest is the study of the cardiovascular function of the subject in relation to body size and to the dimensions of the heart and the vascular system the function may be estimated from the heart rates at submaximal work loads, such as W_{130} as this parameter is related to the dimensional variables and mainly in the same way as in younger men Because of the decline of HR_{max} with age, W_{130} was determined in this study instead of W_{170} which is generally used as functional parameter in this laboratory

When on the other hand the primary interest is the study of the maximal capacity of the subject for exercise of moderate short duration as in the present investigation, the prediction of this capacity from the heart rate during submaximal work loads seems to be of little practical value. Either the arterial lactate concentration should be studied during submaximal exercise or better, a maximal test should be performed, for instance the simple one described here with determination of W_{max}.

Summary

Heart rate (HR_{max}) and work load (W_{max}) at maximal working intensity were determined during stepwise increased work loads on a bicycle ergometer in sitting and supine position and during combined arm and leg work in 27 healthy men aged 61—83 years.

HR_{max} in sitting position decreased with age from 166 beats/min in the 60—69 to 139 beats/min in the 80—83-year group. W_{max} decreased simultaneously from 928 to 650 kpm/min. HR_{max} or W_{max} did not increase significantly when the tests were repeated.

In supine position significantly lower values for HR_{max} and W_{max} were recorded, and the incidence of fatigue in the legs on interruption of the test was higher than in sitting position.

During combined arm and leg work both HR_{max} and W_{max} were significantly higher than during leg work alone. The main reason for this increase seems to be the effect of counterirritation, i.e. the cranking with the arms seemed to suppress the sensations from the legs.

There was a close correlation between W_{max} and the maximal oxygen uptake.

The mean HR_{max} was 158.5 beats/min with a standard deviation of ±13.8 beats/min or ±10.0 % of the mean. By multiple regression analysis with HR_{max} as dependent variable, the residual standard deviation decreased to ±6.1 % with age, working intensity at heart rate 130 (W_{130}) and log arterial lactate concentration at heart rate 130 as independent variables. All the variables had negative regression coefficients (b). The lowest residual standard deviation (± 4.9 %) was obtained when the lactate concentration at maximal working intensity (log $lact_{max}$) was included as independent variable together with the anamnestic degree of physical activity (both with positive regression coefficients), age, W_{130} and the 2—6 min heart rate increase at heart rate 130 (St st_{130}).

The mean W_{max} was 847 kpm/min with a standard deviation of ±170 kpm/min or ±20.1 % of the mean. With W_{max} as dependent variable the residual standard deviation decreased to ±11.8 % when log arterial lactate at 600 kpm/min and age were the two independent variables (negative b's). The lowest residual standard deviation (±8.6 %) was obtained with the same five independent variables as for HR_{max} (St st_{130}, W_{130}, physical activity, log $lact_{max}$ and age), but the regression coefficient for W_{130} now was positive.

Neither body size, heart volume or blood volume were of probable significance when correlated to HR_{max} or W_{max}, nor were lung volumes or measured parameters of ventilatory function. Together with the close relationship between W_{max} and the blood lactate concentration during exercise this suggests that the physical working capacity in these old men was limited by peripheral factors, either vascular or muscular metabolic.

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External Cardiac Massage

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Acute circulatory arrest, either asystole or tachyarrhythmia usually in the form of ventricular fibrillation is a complication that is not unusual in patients with myocardial infarction or ischemic heart disease It can also appear in connection with profound bleeding during anesthesia or when an electrical current passes through the patient It sometimes occurs during such examinations as bronchoscopy gastroscopy esophagoscopy or rectal palpation and may also be provoked by a simple procedure such as arterial puncture Certain therapeutic measures such as enucleation of an eye may produce acute circulatory arrest by means of pronounced vagal reaction During the last few years quite a few cases of severe arrhythmias often with acute circulatory arrest have been reported as a fatal complication to quinidine treatment Changes in the electrolyte balance due to oral diuretics might account for this high rate of complications Acute circulatory arrest also appears in other types of disease It is thus apparent that the treatment of this alarming state should be familiar to general practitioners as well as to cardiologists

Hitherto the treatment of acute circulatory arrest in a medical ward has consisted either of pounding on the patient s thorax or else of masterly inactivity Thoracotomy and internal cardiac massage has been successful in a few cases but there is no doubt that the closed chest cardiac massage described in 1960 by Kouwenhoven et al (5) was a major development

When scrutinizing the literature it may be seen that external cardiac massage is not new As early as 1878 Boehm (2) reported good results with such a method in cats, and Tournade et al (7) was able to produce a satisfactory blood pressure in dogs by compression of their thoracic cage It has also been supposed that the rocking method used for artificial respiration produced a change in the blood pressure of such a size that vital parts of the body received a sufficient blood supply (3) Gurvich and Yuniev

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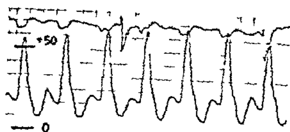


Fig 1 Pressure curve from the femoral artery during external cardiac massage in a patient who had been defibrillated the electrical activity shown in the ECG did not result in mechanical activity Note the electric deformation of bundle branch block type in the ECG after each mechanical compression of the thorax
The pressure figures are in mm Hg The time interval between two heavy lines is 0 1 sec

(4) reported that when ventricular fibrillation was produced in dogs, defibrillation was normally successful only if it was performed within 1 1/2 minutes after the beginning of the ventricular fibrillation This time could be prolonged from 1 1/2 minutes to 8 minutes if the thorax was rhythmically compressed

Method

External cardiac massage was used occasionally in human patients in the 1950 s but it is the merit of the Johns Hopkins team to have used this method more or less routinely in a large number of patients The method is quite simple By applying pressure on the lower third of the sternum the distance between the sternum and the spine is reduced resulting in a compression of the heart It is important to place the pressure on the lower part of the sternum and not on the ribs to avoid rib fractures This rule should be modified only in patients with a pronounced left ventricular hypertrophy with the main part of the heart situated to the left of the sternum The number of compressions should be 60—80 per minute, sometimes more The compression should push the sternum 3—5 cm towards the spine The venous filling of the heart is supported by elevation of the legs and the lower part of the body and by the negative intrathoracic pressure created between the compressions from the resilient expansion of the thorax It is best to have the patient on a firm base such as the floor External cardiac massage is less effective and much harder work when performed with the patient in bed

Effectiveness of external cardiac massage

It has been claimed that external cardiac massage is ineffective, but with this method it seems possible to supply vital parts of the body with enough blood An effective external cardiac massage produces a contraction of dilated pupils It is possible to palpate a good pulse in the femoral and carotid arteries as also in the radial arteries during an effective cardiac massage in humans and blood pressure recordings with systolic values of 100—150 mm Hg are satisfactory We determined the arterial blood oxygen tension values in ten patients to establish that the external cardiac massage was effective Arterial oxygen tension values were normal in five patients and slightly decreased in five No value was below 51 mm Hg (the normal range with the method used is 83—104 mm Hg) Normal values were found in three survivors and two who died in connection with external cardiac massage Subnormal values were obtained in one survivor and four who died in connection with the massage Arterial pressure recordings were made in some patients during the massage (fig 1)

It has been discussed whether external or internal cardiac massage is the more effective Redding and Cozine (6) have compared external and internal cardiac massage in dogs and concluded that they were equally effective Our own experience from human patients in whom both external and internal cardiac massage has been performed is that external cardiac massage is as effective as the internal approach and we think that even if a patient develops acute circulatory arrest in the operating theatre,

TABLE I

Diagnosis	No of pat	Dead in connection with cardiac massage	Survivors	Discharged
Myocardial infarction	26	14	12	2
Ischemic heart disease	23	9	14	4
Myocarditis + acquired heart disease	2	2	—	—
Cardiac decompensation + pulmonary insufficiency	2	1	1	—
Adams-Stokes attacks	1	—	1	1
Quinidine intoxication	1	—	1	1
Intraperitoneal hemorrhage	1	—	1	1
Acute circulatory arrest during anesthesia and bronchoscopy or esophagoscopy	4	2	2	2
Cerebral hemorrhage	1	1	—	—
Acute circulatory arrest during eye enucleation	1	—	1	—
Aortic stenosis	1	1	—	—
Drowning	1	—	1	1
Barbiturate intoxication	1	—	1	1
Total	65	30	35	13

external cardiac massage should first be performed — always providing that the chest is not already open It is very important to establish during external cardiac massage that the pupils are contracted and that there is a good pulse palpable in the femoral and carotid arteries Massage has often been unnecessarily long in taken effect because these parameters were not considered A slight change of the position of the hand on the thorax is sometimes sufficient to improve the effect of the massage It should be borne in mind that morphine given before the massage will produce a persistent miosis even during unsatisfactory cerebral circulation

Material

Our series now includes 65 patients (table I) This series comprises all consecutive patients with acute circulatory arrest in the medical wards in whom external cardiac massage has been used Patients with acute circulatory arrest in the operating theatre with two exceptions and in the post-operative ward have thus not been included To get familiar with the method we had very wide indications for external cardiac massage early in the series we are now more selective The age distribution is shown in table II As is seen from table I most patients have had a heart disease but the diagnoses are varying Most patients have been compensated but in two the acute circulatory arrest appeared during a pulmonary edema one of these died and the other survived but later died in a new acute circulatory arrest

TABLE II

	Age in years	
	Mean	Range
Total no. of patients	59	19–82
Dead in connection with external cardiac massage	58	19–82
Survivors	61	44–79
Discharged	55	32–67

TABLE III. Complications

	No. of patients	
	Total material (65)	Survivors (35)
Rib fractures, single or multiple	34	8
Fracture of sternum	9	1
Bone marrow emboli	5	–
Liver injury	5	1
Mucosal erosions in esophagus or stomach	1	–

In the total material 30 of the 65 patients died in connection with external cardiac massage. This means that they never regained a spontaneous satisfactory blood pressure. *Thirty-five patients survived of whom 13 could be discharged from hospital.* The mean age of the discharged patients is slightly lower than for the other group (table II).

Nine patients among those who survived but were not discharged from the hospital remained unconscious after the massage. They all died during the following three days. Among those who regained consciousness after the massage six died within the first week, one after two weeks, one after three weeks and five lived four weeks or longer. Most of these patients died in a new acute circulatory arrest.

Complications

The commonest complication of external cardiac massage is either single or multiple rib fractures, which occurred in 34 of our patients (table III). In 9 patients a fracture of the sternum appeared, while 5 patients showed bone marrow emboli in the pulmonary vessels, a small number in four patients and more abundant in the fifth. This last patient was given external cardiac massage 26 times in two days and defibrillated 15 times. In 4 patients there were small subcapsular hematomata on the liver surface. In another patient there was a rift in one of the liver ligaments, with liver laceration resulting in an intraperitoneal hemorrhage of 500 ml blood. This was the only severe complication. The patients who died had often been massaged for longer periods resulting in comparatively greater trauma. The complications are fewer and less severe in the survivors (table III). Only 2 of the discharged patients have had any complications. These were minor rib fractures which did not prove particularly distressing.

Some patients in whom cerebral sequelae remained after the external cardiac massage were cooled to a rectal temperature of about 30° C to decrease the brain volume and thus the intracranial pressure. It is doubtful if the hypothermia had any beneficial effect on the cerebral condition and difficult to reach any definite conclusions from this small material.

Factors of importance for the prognosis

It is often difficult to decide when to stop the external cardiac massage I have therefore tried to analyze the importance of different factors for the prognosis There is a significant difference between patients getting the acute circulatory arrest outside the hospital and those in whom it appears after the hospitaliza tion Table IV shows that the percentage of survivors is much higher among those who arrived conscious and nearly all of those who were discharged were conscious on admittance Of the survivors who were conscious on admission to hospital 23 regained consciousness after massage while 5 did not Two of the patients who were unconscious on admission to hospital regained consciousness after massage while 5 did not The prognosis is worse when the external cardiac massage has to be continued for a long time Table V shows that when the massage continues for more than half an hour the prognosis is extremely bad None of these patients was discharged The type of arrhythmia is of some importance Table VI shows that patients with bradyarrhythmia have a somewhat better prognosis than those with ventricular fibrillation The defibrillation was performed with an Elema alternating current defibrillator If one shock was unsuccessful a series of three shocks were given usually of 400 V or 500 V

In some cases the electrocardiographic changes such as bundle branch block developing during the circulatory arrest remained quite a long time and it is apparent from table VII that the prognosis for these cases is much worse than

TABLE IV State of consciousness at hospitalization

No of patients		Dead in connection with cardiac massage		Survivors		Discharged	
A	B	A	B	A	B	A	B
51	14	23	7	28	7	12	1

A = conscious B = unconscious

TABLE V Duration of external cardiac massage

No of patients		Dead in connection with cardiac massage		Survivors		Discharged	
A	B	A	B	A	B	A	B
18	15	2	12	16	3	7	0

A = Duration < 0 5 hour B > 0 5 hour

TABLE VI *Prognosis* for patients with ventricular fibrillation and bradyarrhythmia respectively

No of patients		Dead in connection with cardiac massage		Survivors		Discharged	
VF	BA	VF	BA	VF	BA	VF	BA
41 (3)	18 (3)	25	5	16 (3)	13 (3)	4 (2)	5 (2)

VF = ventricular fibrillation BA = bradyarrhythmia including asystole

Figure in brackets means that it is uncertain if the arrhythmia was ventricular fibrillation or bradyarrhythmia.

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Figure in brackets means that it is uncertain if the arrhythmia was ventricular fibrillation or bradyarrhythmia

TABLE VII Importance for prognosis of time for regress of ECG changes

No of patients		Dead in connection with cardiac massage		Survivors		Discharged	
A	B	A	B	A	B	A	B
14	16	1	13	13	3	4	0

A = comparatively rapid regress (usually within half an hour) B = comparatively slow regress including persistent ventricular fibrillation

for those in whom the electrocardiogram returned rapidly to normal The diagnosis (table I) and age are of prognostic importance, too, but naturally the most important factor is the duration of the circulatory arrest It is often difficult to establish just how long the circulatory arrest has existed, but in all the patients who were discharged its duration was comparatively short It is also remarkable that all the discharged patients have been hospitalized with one important exception a 32-year-old man who fell from his boat into the sea By chance he was found by a competent thoracic surgeon after 1 1/2—2 hours deeply unconscious and hypothermic By means of artificial respiration and external cardiac massage he survived and is now in good condition He has no cardiac sequelae

Follow-up

One matter of concern to us is the survival of patients with severe cerebral lesions In no case did this occur Those survivors who never regained consciousness died within a comparatively short time, none of them living for more than a few days As mentioned earlier many of the survivors died some weeks after the massage, often in another circulatory arrest Perhaps these patients should routinely receive prophylactic anti arrhythmic treatment

Thirteen patients were discharged from hospital Two of these with ischemic heart disease died suddenly 8 months and another 20 months after the acute circulatory arrest, probably due to a new attack of ventricular fibrillation Another patient died 3 1/2 months after the operation, during which the acute circulatory arrest appeared, in consequence of surgical complications to his first operation The other patients are still alive and apparently in good condition It is important to be sure that no severe brain damage has developed during the circulatory arrest To determine the degree of this possible brain damage we have made the following tests on patients (Bengtsson, Hansson and Johansson (1) unpublished observations)

1 Electroencephalogram
2 Tests especially constructed to detect brain damage
3 Psychiatric examination of brain function

The EEG was normal in all cases Psychological tests showed reduced spatial visualization and recognition capacity but visual speed and flexibility and finger dexterity were unchanged Psychiatric examination was made in most of the cases Normal findings were obtained in a third of the patients, another third showed signs of slight impairment and the remainder had severe brain damage

One should remember that many of these patients are of an age when it is reasonable to suspect that atherosclerosis may have already produced brain damage before the cardiac massage, and that neurological changes regress rather slowly. Many of our patients were assessed shortly after the acute circulatory arrest. In younger patients cerebral symptoms, even if pronounced, can disappear. This was so in a 48-year old woman with repeated attacks of circulatory arrest, one of a duration of seven minutes and treated by internal cardiac massage (performed by Dr Ryd in 1957). The patient was unconscious for 24 hours after the massage and then very agitated. A paralysis of her right arm disappeared after a few days. Amnesia for the time after the massage gradually disappeared and her recognition and concentration capacity, which was badly damaged as judged from psychological tests, improved during five months after the circulatory arrest. At follow up four years after the massage she felt quite well and a neurological examination was normal.

Metabolic acidosis during acute circulatory arrest

We obtained blood samples from some of the patients who received external cardiac massage to determine the oxygen and carbon dioxide tension, the pH and the standard bicarbonate, and found that a metabolic acidosis had developed very rapidly. It is known from the literature that catecholamines such as noradrenaline are less effective at a low pH than at a normal one. The low pH found in our patients might possibly explain the fact that in some of them it was not possible to keep blood pressure at a satisfactory level. So we routinely tried to raise the pH to normal with sodium bicarbonate, the infusion of which usually kept the blood at normal pH. This routine developed from studies in dogs. These studies established that metabolic acidosis develops in a few minutes when the animals are subjected to circulatory arrest after three minutes followed by external cardiac massage. Sodium bicarbonate as a 5 per cent solution and THAM (trishydroxymethylaminomethane) were found to be more effective than molar lactate in keeping the pH within normal values.

Alkalinizing agents intravenously are now a routine medication in patients with acute circulatory arrest.

Indications for external cardiac massage

It is difficult to decide who should receive external cardiac massage. It is obvious that external massage should not be used in an old cachectic patient with a metastasizing malignant disease. It is as obvious that external cardiac massage should be used in a middle aged patient with ischemic heart disease but in otherwise good condition. Between these two types lies a large group where opinions can differ. It is impossible to make strict rules but I think it can be of value to argue in the following way. If acute circulatory arrest occurs in a patient in whom there are indications for therapeutic or major diagnostic procedures cardiac massage should be performed.

The most important factor is how long the circulation has been stopped. If the arrest has existed for more than 4—6

minutes resuscitation should not be attempted because the risk of severe brain damage is too high Often it is not known how long the circulatory arrest has existed If there is reason to suspect a comparatively short duration we begin with external cardiac massage If after 10 minutes of effective massage and effective artificial ventilation with pure oxygen the patient shows no response such as contraction of pupils spontaneous breathing or spontaneous heart activity, there is no point in continuing

Signs indicating an impending acute circulatory arrest

Obviously the duration of circulatory arrest is of the greatest importance for the outcome Ideally all patients in whom there are grounds for suspecting the development of acute circulatory arrest should be kept together under continuous supervision To minimize the number of patients needing such extended supervision, it is essential to know the signs of an impending acute circulatory arrest To this end we have studied 174 consecutive cases with signs of myocardial infarction Electrocardiograms and routine laboratory data were recorded at different intervals in these patients None of these signs were of value in predicting the appearance of an acute circulatory arrest The arterial blood pH seems to be the only laboratory finding of some value for the prognosis All our patients who have survived have had a normal arterial pH, and in some of them signs of hyperventilation appeared, while half of those who died have had a low arterial pH

There is no doubt that external cardiac massage is a valuable method for the prolongation of life It may be said that some of the patients who survived would have done so without the massage This is possible in some of the patients with Adams-Stokes attacks But we have seen enough patients with long standing ventricular fibrillation who have responsed well to the massage and defibrillation to be convinced that this a valuable method in the doctor's therapeutic arsenal On the other hand its value should not be overestimated the disease producing the acute circulatory arrest remains and can cause another attack which might be fatal

Summary

External cardiac massage as described by Kouwenhoven et al (5) has been used on 65 patients in our medical ward Thirty of these patients died in connection with the cardiac massage while 35 survived, 13 of whom were discharged from the hospital The commonest complication to external cardiac massage was rib fractures The one severe complication was a rift in a liver ligament with hepatic laceration and a resulting intraperitoneal hemorrhage

Among noteworthy prognostic factors, the most important is the time between the appearance of the acute circulatory arrest and the beginning of the cardiac massage The percentage of survivors was much higher among those who arrived conscious at the hospital The prognosis worsens when the external cardiac massage has to be continued for a long time and when the electrocardio-

graphic changes developing during the acute circulatory arrest remain for a long time Patients with bradyarrhythmia have a better prognosis than those with ventricular fibrillation

None of the discharged patients showed signs of severe brain damage attributable to unsatisfactory circulation during the external cardiac massage

Metabolic acidosis developed very rapidly after the appearance of the acute circulatory arrest The acidosis was best combatted with sodium bicarbonate or THAM (trishydroxymethylaminomethane)

Good arterial pressure curves were obtained during external cardiac massage, and the arterial oxygen tension values obtained from some patients during the massage were mostly normal

Various laboratory data were examined to find a significant sign indicative of impending acute circulatory arrest in patients with myocardial infarction The only sign which seemed to be of some value was a lowered arterial blood pH

It is concluded that external cardiac massage may be a valuable method of resuscitation with which every physician should be familiar Its value should not be overestimated, however The underlying disease producing the arrhythmia will remain and might produce another attack of acute circulatory arrest

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Dynamic Spirometry in Patients with Tracheal Stenosis

By

H Engstrom, G Grimby and B Soderholm

The ventilatory capacity in subjects with a stenosis of larynx and trachea is often seriously impaired There are reports for a few subjects that the inspiratory flow is more reduced than the expiratory flow (2, 4, 9) The present investigation was performed in order to study the airway resistance before and after tracheotomy In some subjects static lung volumes were measured in order to evaluate the effect of prolonged breathing against a markedly increased airway resistance

Material

The patients studied varied in age between 16 and 95 (mean age 58) 22 were men and 19 women Seventeen patients were on the same occasion investigated both when breathing through the mouth and when breathing through a tracheal cannula of the largest possible bore The other patients were studied only while breathing through the mouth The etiology of the tracheal stenosis is shown in table 1

Twenty three of the patients had a stenosis with a fixed non resilient wall like a cicatrix or a tumor and 18 had a stenosis with a cross sectional area that was found to vary during breathing as judged from laryngoscopy

Since no data were available concerning the normal distribution of the forced inspiratory capacity a group of 38 clinically healthy men in the age range 21—61 (mean age 41) were studied In this group were included well trained athletes as well as sedentary men, in order to study the relationship between forced expiratory and forced inspiratory volumes in one second both at ordinary and at extreme flow rates

Methods

Dynamic spirometry was performed with a modified Bernstein spirometer as described by Berglund et al (3) (the terminology used is as recommended by English respiratory physiologists)

In addition to the usual procedure two or three forced inspirations were also performed (forced inspiratory vital capacity) and the forced inspiratory volume in one second ($FIV_{1.0}$) was measured The maximum voluntary ventilation was determined with a frequency chosen by the subject and denoted MVV_F (6)

In some cases the functional residual capacity (FRC) was also measured with the closed helium-dilution method (6) The intrapulmonary distribution was analyzed

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TABLE I. The etiology of the tracheal stenosis

	♂	♀
Recurrent nerve palsy, one side	3	3
Recurrent nerve palsy, both sides	2	9
Synechia of vocal cords after trauma or operation	2	1
Tumor of larynx or trachea or compression or stenosis over some length	12	6
Stenosis and recurrent nerve palsy	3	0

by the single breath technique, with measurement of the difference in nitrogen concentration between 750 ml and 1 250 ml expired air after inhalation of one liter oxygen (10).

Results

In table II are given the results for the control group. $FEV_{1.0}$ and $FIV_{1.0}$ expressed as a percentage of the vital capacity (FEV % and FIV % respectively) were *found not to be related to* age. Only 7 of 38 control subjects had a $FIV_{1.0}$ that was lower than the forced expiratory volume in one second ($FEV_{1.0}$).

The spirometric values from the patients were expressed as percentage of the predicted normal value (6). The whole material is presented in fig. 1. Vital capacity (VC) and $FEV_{1.0}$ were normal or low, averaging 80 % and 66 % respectively of the predicted normal value. MVV_F, however, was decreased in all patients by more than 25 % of the predicted normal value, the mean decrease being 65 %. As seen in fig. 2 the total lung capacity (TLC) was fairly normal in all cases studied, the mean value being 102 %. Thus FRC was above the predicted normal value in most cases (mean value 120 %). Single-breath nitrogen test did not reveal any impairment of mixing.

It is well known that there is a linear correlation between $FEV_{1.0}$ and MVV in normal subjects (see e.g. 6). Fig. 3 illustrates that in patients with a tracheal stenosis MVV_F is relatively more reduced than would be predicted from the fairly *normal* $FEV_{1.0}$. *When the patients were* breathing through the tracheal cannula an increase was noted both in MVV_F and $FEV_{1.0}$, but in several patients MVV_F increased more than $FEV_{1.0}$, thus the relationship between these two parameters became more parallel to the normal one (fig. 4).

TABLE II. *Results from a control group of 38 clinically healthy men in the age range 21—61.* The normal range of FEV % and FIV % is shown in figs. 5 and 6.

	VC		$FEV_{1.0}$				
	l	% of predicted normal value¹	l	% of predicted normal value¹	FEV %	$FIV_{1.0}$ l	FIV %
Mean	5 15	103	4 18	110	82	4 71	91
Range	3 70 – 6 64	85 – 120	3 00 – 5 27	97 – 136	71 – 94	2 69 – 6 20	67 – 99

¹ According to Grimby & Soderholm (6).

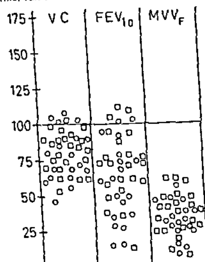


Fig 1 Vital capacity (VC) forced expiratory volume in one second ($FEV_{1.0}$) and maximum voluntary ventilation (MVV_F) for all patients in per cent of normal value predicted according to Grimby & Soderholm 6) □ males ○ females

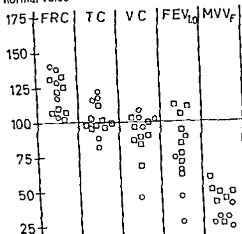


Fig 2 Functional residual capacity (FRC) total lung capacity (TLC) VC $FEV_{1.0}$ and MVV_F in 13 patients in per cent of the normal value predicted according to Grimby & Soderholm (6) □ males ○ *females*

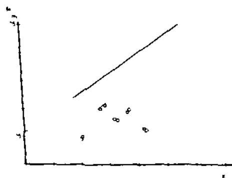


Fig 3 MVV_F in relation to $FEV_{1.0}$ in patients with tracheal stenosis. Straight lines indicate normal regression between these parameters ± S D from 6 □ males ○ females.

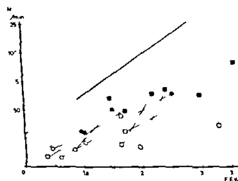


Fig 4 MVV_F in relation to $FEV_{1.0}$ in patients with tracheal stenosis breathing through the mouth (open symbols) and through a tracheal cannula (filled symbols) Straight lines indicate the normal regression as in fig 3 □ males, ○ females.

In 27 of 31 patients with tracheal stenosis $FIV_{1.0}/FIV$ % was lower than $FEV_{1.0}/FEV$ % (fig 5) When the patients were breathing through a tracheal cannula instead of through the mouth there was in some cases a more pronounced increase in FIV % than in FEV % (fig 6) which is reflected in the larger increase in MVV_F than in $FEV_{1.0}$ as demonstrated in fig 4

No difference was found in the spirometric values between those patients

TABLE I. The etiology of the tracheal stenosis

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Recurrent nerve palsy, one side	3	3
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	l	% of predicted normal value¹	l	% of predicted normal value	FEV %	$FIV_{1.0}$ l	FIV %
Mean	5.15	103	4.18	110	8[illegible]	4.71	91
Range	3.70–6.64	85–120	3.00–5.27	97–136	71–94	2.69–6.20	67–99

¹ According to Grimby & Soderholm (6).

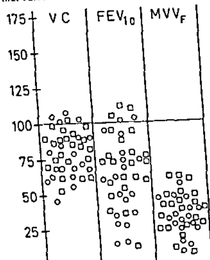


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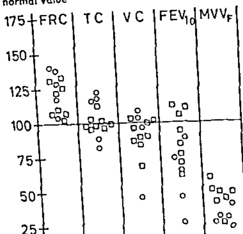


Fig 2 Functional residual capacity (FRC), total lung capacity (TLC), VC, FEV_1 and MVV_F in 13 patients in per cent of the normal value predicted according to Grimby & Soderholm (6). □ males ○ females.



Fig 3 MVV_F in relation to $FEV_{1.0}$ in patients with tracheal stenosis. Straight lines indicate normal regression between these parameters ± S.D. for men (6). □ males ○ females.

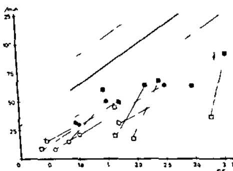


Fig 4 MVV_F in relation to FEV_1 in patients with tracheal stenosis breathing through the mouth (open symbols) and through a tracheal cannula (filled symbols). Straight lines indicate the normal regression as in fig 3. □ males ○ females.

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No difference was found in the spirometric values between those patients

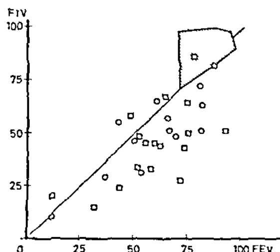


Fig 5 Forced inspiratory and forced expiratory volume in one second in per cent of the vital capacity (FIV % and FEV % respectively) in patients with tracheal stenosis The hatched area represents the normal range as judged from the control group The line of identity is drawn □ males ○ females

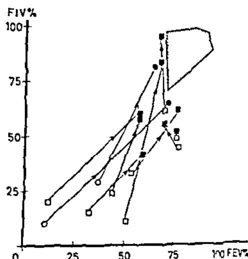


Fig 6 FIV % and FEV % in patients with tracheal stenosis breathing through the mouth (open symbols) and through a tracheal cannula (filled symbols) The hatched area represents the normal range as judged from the control group. ■←—□ males ●←—○ females

who had a fixed (cicatricial) stenosis and those in whom the stenosis was found to vary during breathing as judged by laryngoscopy

Discussion

In normal subjects there is a good correlation between the forced expired volume in one second and the maximum voluntary ventilation The same relationship is also found in patients with increased expiratory flow resistance In asthmatics bronchodilatation causes a parallel increase in $FEV_{1.0}$ and MVV_F (Grimby and Söderholm, unpublished observations) In the present studies, however, there is a marked discrepancy between the forced expired volume and the maximal voluntary ventilation The reason for this deviation from normality seems to be reduction in inspiratory flow In our normal subjects the forced inspiratory volume in one second was higher than the forced expiratory volume in 31 out of 38 subjects, whereas in the group of patients with a tracheal stenosis only 4 of 31 had a $FIV_{1.0}$ higher than $FEV_{1.0}$ This reduction in inspiratory flow capacity has previously been observed by Arbore et al (2) and Bonnet et al (4)

In our subjects partial release of the obstruction by tracheotomy in half of the cases studied caused a more pronounced increase in $FIV_{1.0}$ than in $FEV_{1.0}$ and similarly MVV_F increased more than might be expected from the change in $FEV_{1.0}$ Thus the effect of an obstruction situated in the upper part of the tracheal bronchial tree seems to be a more pronounced reduction in inspiratory than in expiratory flow capacity, in spite of the fact that the resistance at a given flow must be similar We have no indication that surface tension forces

TABLE III Pressure-head values with different airway diameters and flow rates calculated from figures given by Ingelstedt & Toremalm (7)

Diameter mm — corresponding to	Pressure drop (mm Hg) in tracheal model calculated at constant flow (l/sec) 0 5	2	4
16 mm — larynx	0 1	0 9	4 2
8 mm — cannula	0 4	6 7	26 5
5 mm — stenosis	4 6	36 0	141 8

appreciably affect the resistance in tracheal stenosis since fixed and movable stenoses behaved similarly A more probable explanation becomes apparent when the mechanics of breathing are considered

Ingelstedt and Toremalm (7) studied air flow patterns in the respiratory tract using a model of the trachea To this model were attached constrictions of different diameters chosen so as to correspond to the cross sectional area of the human larynx to an ordinary tracheal cannula and to a severe tracheal stenosis

Table III has been calculated from their figures using the equation

$$p = k_1 V + k_2 V^2$$

where p pressure in mm Hg V = flow in l sec and k_1 and k_2 are constants for laminary and turbulent flow respectively

The flow rates have been chosen to represent peak flow rates for quiet to forced breathing Turbulence accounts for about 90 per cent of the pressure drop even at a volume flow of 0 5 l/sec with diameters of 8 mm or less At higher flow rates this is the case even in the trachea Thus the pressure drop necessary for a given flow increases very rapidly when the diameter decreases

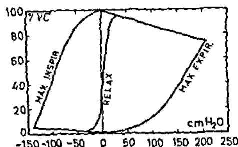


Fig 7 Pressure volume diagram of the chest and lungs according to Agostoni (1)

These calculated pressures should be compared to those which are available for respiratory work Fenn (5) described the pressure-volume diagram of the chest and lungs, and fig 7 shows such a diagram as modified by Agostoni (1) We have chosen this diagram for the discussion since the maximum pressures are in better accordance with those given by Ringqvist (max inspiratory pressure 142 cm H_2O max expiratory pressure 243 cm H_2O in a group of normal men 20—35 years of age, personal communication)

It is obvious that the maximum pressure available for expiration (max expiratory minus relaxation pressure) at functional residual capacity is much higher than the maximum inspiratory pressure Since

work = pressure × volume

the total amount of work which can be performed during inspiration is accordingly lower

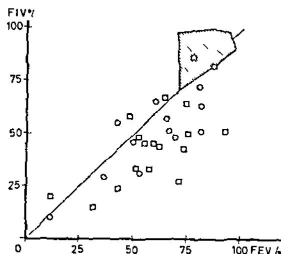


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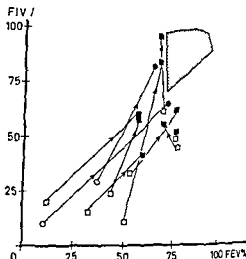


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First Medical University Department (Head C Holten, M D), Department of Thoracic Surgery (Head T Søndergaard) and Department of Clinical Biochemistry (Head R Keiding M D) Kommunehospitalet, Aarhus, Denmark

Albumin Turnover and Thoracic-duct Lymph in Constrictive Pericarditis

By

V Posborg Petersen and Poul Ottosen

Recently it has been reported that hypoalbuminaemia in cases of constrictive pericarditis is due to an abnormal loss of albumin into the gastrointestinal tract (6 7, 11) In one case studied by us (16) intestinal protein loss was associated with intestinal lymphangiectasia which was thought to result from protracted high pressure in the thoracic duct and the intestinal lymphatic apparatus

In the present paper further studies are reported on the relationship between albumin turnover and the composition and transport function of the intestinal lymph as revealed by investigations of thoracic duct lymph in cases of constrictive pericarditis

Material and methods

The patient series as shown in table I consists of six cases of constrictive pericarditis with varying degrees of congestive failure and duration of the disease Case 1 which has been reported in detail elsewhere (16) had a recurrence of oedema six years after a successful pericardiectomy there being only a slightly elevated venous pressure Fluid retention was resistant to mercurial diuretics while combined treatment with spirolactone and chlorothiazide produced a sodium diuresis so that only mild oedema was present at the time of study Clinical signs of considerable fluid retention were present in cases 2 4 5 and 6 while patient no 3 was free of oedema and ascites when studied Results of right heart catheterization compatible with constrictive pericarditis were obtained in all cases and the diagnosis subsequently proved by surgical intervention and treatment

Albumin metabolism was studied with ^{131}I albumin and turnover and pool sizes were calculated according to Pearson et al (15) The results obtained were compared with normal standards as reported by Jarnum and Schwartz (12) In three cases (nos 1 3 5) intestinal permeability was examined by testing with ^{131}I labelled polyvinyl pyrrolidone as described by Gordon (10) Faecal activities were measured for five days, excretions below 1 % of the injected dose were considered normal

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In normal subjects inspiratory work comprises about 1/5 of the total work during maximum ventilation, but in tracheal obstruction the work consumed by the stenosis far outweighs that by the chest and lungs and is shared equally between inspiration and expiration This will equalize inspiratory and expiratory work and thus total ventilation becomes markedly reduced In this connection it should be mentioned that the present material does not include cases with extreme resilient stenosis, i e cases ready for acute tracheotomy Further studies are here necessary to permit a comparison of FEV % and FIV %

In some of our cases total lung volume was determined in order to evaluate the effects on the lungs, if any, of prolonged breathing against a resistance The total lung volume was within normal limits but the functional residual capacity was increased This was interpreted as a state of hyperinflation, since expiratory flow pattern during tracheotomy was almost normal and a single-breath nitrogen test did not reveal any impairment of mixing

Summary

Fourty one cases of stenosis of the upper airways have been studied with dynamic spirometry

Marked reductions in forced inspiratory volume in one second and in maximum voluntary ventilation were consistently found

The forced expiratory volume was less often reduced

The mechanics of breathing are discussed

Acknowledgement

This investigation was supported by a grant from the Swedish National Association against Heart and Chest Diseases

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TABLE I Patient series

Case no	Sex	Age (yrs)	Duration of symptoms (yrs)	Venous pressure (cm)	Oedema	Ascites
1	♂	50	25	12	+	—
2	♀	55	?	21	+	+
3	♂	41	2	31	—	—
4	♂	58	10	25	+	—
5	♂	56	2	27	+	—
6	♂	38	4/12	33	—	+

TABLE II Pressure and flow measurements in patients and control subjects

Case no	Lymph pressure (cm)	Lymph flow (ml/kg/hr)
1	25	3 1
2	22	[1]1 1
3	33	4 9
4	24	4 8
5	30	7 3
6	34	—
Control	6	0 6
Control	7	1 1
Control	6	1 5

[1] Incomplete collection

Lymph was obtained after cannulation of the thoracic duct with a polyethylene catheter under local anaesthesia according to the technique described by Linder and Blomstrand (14) During the collection of lymph the patients were confined to bed After a control period of 2 hours 200 ml of cream with 18 % fat was administered with a tracer dose of 30—50 μC ^{131}I labelled oleic acid in gelatine capsules Food was withheld for 16 hours after the high fat meal while fluid was given ad lib In all the isotope studies the thyroidal uptake of ^{131}I was blocked by oral administration of stable iodine Radioactivity was measured in a scintillation counter connected with a Tracerlab Superscaler

In each case, the pressure in the thoracic duct was measured by the height above the sternum of the lymph column with the patient in horizontal position The flow rate of duct lymph was recorded by continuous collection in 2- and 4-hour periods and additional samples were taken at the end of each period Chemical analyses for lipids and proteins were performed as previously described (16) Transitory hypotension due to high flow rates occurred in case 1 after 24 hours, and in case 3 lymph collection was discontinued after 7 hours when the blood pressure tended to fall Accordingly, human serum was infused intravenously in case no 4 and 5 in quantities corresponding to the volume of lymph produced during each preceding collection period Quantitative collection of lymph was possible in only four of the six patients (nos 1 3, 4 5) due to the absence of a single trunk in the cervical part of the thoracic duct In cases 2 and 6 two or three smaller branches were found, each separately joining the internal jugular vein In both cases the largest of these vessels was cannulated and the pressure obtained Lymph was collected in case 2 but obviously lymph escaped through at least one additional channel In case 6 the catheter was removed shortly after insertion as free flow ceased Lymph studies were also carried out in three control subjects in whom cannulation was done following a supraclavicular and mediastinal biopsy of lymph nodes. These patients were investigated because of a solitary lesion in the left upper pulmonary lobe which proved benign in the first two cases but malignant in the third, although no metastases were present As far as could be judged none of these lesions extended beyond the lung parenchyma and the mediastinal structures appeared normal on radiographs. The same procedure as outlined above was followed in these control subjects except that replacement of lymph by human serum was not considered necessary as flow rates were much lower than in patients with pericarditis

Fig 1 Thoracic duct lymph flow — patients —controls

Fig 2 Relationships between concentrations of protein fractions in lymph and serum ● patients ○ controls

Results

In patients with constrictive pericarditis flow rates and lymph pressure were greatly increased as compared with control subjects (table II) in whom flow rates ranged from 0 6 to 1 5 ml/kg/hour — which agrees with previous findings in two normal subjects with thoracic duct fistulae (4 5) and in cases of advanced malignant disease (1) While the lymph from control subjects appeared thick and milky white that from patients with pericarditis was watery opalescent and slightly haemorrhagic The presence of red cells probably due to high capillary pressure with haemorrhage per diapedesim was also noticed by Starling (17) in duct lymph from dogs with experimental portal vein obstruction

In all animal species including man the flow of lymph in the thoracic duct occurs continuously irrespective of diet or whether or not the dietary state is postabsorptive (19) In the present series the flow of thoracic duct lymph occurred at an almost constant rate (fig 1) throughout the collection period and was unaffected by the ingestion of fat after the initial 2 hour control period In normal resting animals no appreciable lymph flow occurs from structures other than the liver and the gastrointestinal tract The relative contribution of these areas to duct lymph was studied in the dog by Cain et al (3) who found that hepatic lymph supplied one fourth to one half of the total volume while intestinal lymph made up the remaining part of thoracic duct lymph

Protein studies

Serum albumin was decreased in three patients (cases 1 2 4) and within nor

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TABLE II. Pressure and flow measurements in patients and control subjects

Case no	Lymph pressure (cm)	Lymph flow (ml/kg/hr)
1	25	3.1
2	22	[1]1.1
3	33	4.9
4	24	4.8
5	30	7.3
6	34	—
Control	6	0.6
Control	7	1.1
Control	6	1.5

[1] *Incomplete collection.*

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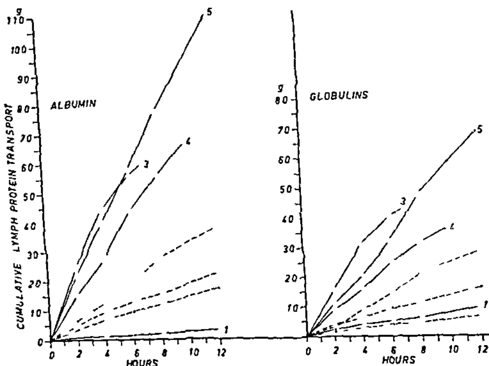


Fig 3 Cumulative transport of albumin and of globulins with thoracic duct lymph — patients controls

gastrointestinal loss of albumin as indicated by an increased faecal excretion of radio-iodine while in patients with normal serum albumin there was no evidence of intestinal albumin loss The amount of circulating albumin was low in patients with hypoalbuminaemia while in all but one case (no 1) the total albumin pool was within normal limits due to a rather large extravascular pool In one patient (case 6) without hypoalbuminaemia total protein was even increased above normal due to a high extravascular proportion As expected extravascular pool sizes were highest in those patients with large fluid retentions The fractional turnover rate (albumin degradation) was much increased in two patients with hypoalbuminaemia and at the upper normal limit in further two cases Albumin production as indicated by the absolute amount turned over per day was increased in only one patient with intestinal loss and at the upper normal limit in one without

The extravascular circulation of proteins in patients with constrictive pericarditis and in control subjects with cannulated thoracic ducts appears from fig 3 which shows cumulative transports of albumin and globulin Due to the very high flow rates the lymphatic transport of albumin was higher in patients than in control subjects except in case 1 in

TABLE III Lymph protein fractions in patients and control subjects

Case no	Constrictive pericarditis					Controls		
	1	2	3	4	5	1	2	2
Total protein (g%)	0 9	3 2	5 1	3 4	4 6	5 3	5 4	4 5
Albumin (g%)	0 2	1 6	3 1	2 1	3 2	3 8	3 6	2 8
α globulin (g%)	0 2	0 5	0 6	0 4	0 3	0 6	0 7	0 6
β globulin (g%)	0 2	0 5	0 6	0 4	0 4	0 4	0 7	0 5
γ globulin (g%)	0 3	0 6	0 8	0 5	0 7	0 5	0 4	0 6
α lipoprotein (%)	23	14	17	22	44	9	18	24
β lipoprotein (%)	77	86	83	78	56	81	82	76

TABLE IV Albumin turnover

	Case no						Normal (SD)
	1	2	3	4	5	6	
Serum albumin (g/100 ml)	1 3	3 0	5 0	3 0	4 1	5 0	4 5 (0 25)
Total albumin (g/kg)	1 1	4 2	5 8	4 9	—	7 0	4 4 (0 30)
Circulating alb (g/kg)	0 48	1 17	2 79	1 54	—	2 36	2 12 (0 32)
Extravascular alb (% of total)	54	72	52	60	—	67	58 (5)
Albumin degradation (% of circulating/day)	29	12	7	23	—	12	10 (2)
Albumin turnover (mg/kg day)	139	143	203	356	—	284	206 (36)
Faecal output of ^{131}I (% of dose in 5 days)	0 92	0 88	0 17	2 22		0 15	<0 40
^{131}I PVP test	9 2	—	0 44	—	0 94	—	<1 0

mal limits in the remaining three (table IV) All the protein fractions of serum as determined by paper electrophoresis are present in lymph although at lower levels (table III and fig 2) The relationship between proteins in lymph and in serum as reflected by the lymph serum ratios showed that in most patients lymph proteins were present in lower concentrations relative to serum proteins than in control subjects

Albumin turnover studies (table IV) revealed that hypoalbuminaemia in each case was associated with an increased

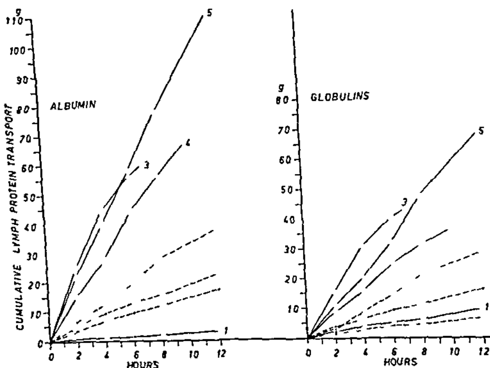


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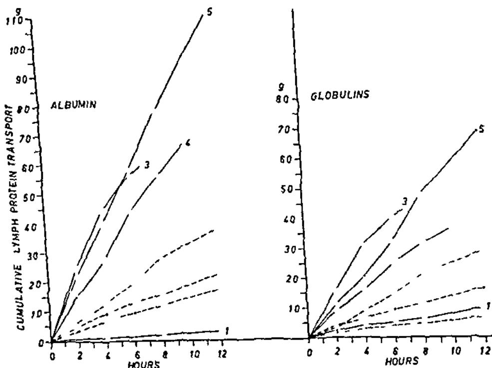


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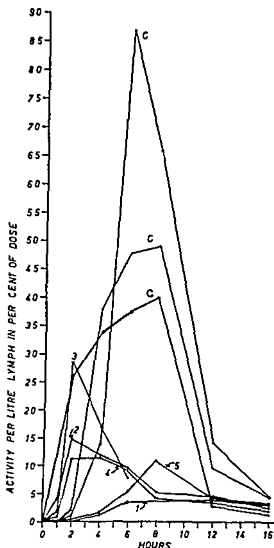


Fig 4 Lymph activities after ingestion of ^{131}I oleic acid Figures indicate patients C control subjects

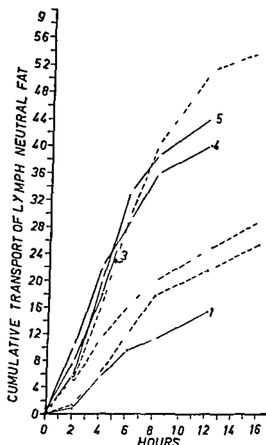


Fig 5 Cumulative transport of lymph neutral fat after ingestion of cream — patients — — controls

whom the lymph albumin concentration was extremely low Among the three remaining patients, one (case 4) with increased intestinal albumin loss carried only slightly lower amounts of albumin with the duct lymph than two patients without intestinal albumin loss The lymphatic transport of globulin was similar in pattern to albumin transport, except that case 1 came within the range of the control subjects due to a less reduced lymph globulin concentration

Lipid studies

The transfer of ^{131}-I oleic acid as measured by the concentrations of the tracer in duct lymph is shown graphically in fig 4 In control subjects concentrations rose to peak values at 6—8 hours and decreased to near initial values after 16 hours On the other hand, concentration curves for the patients took a more irregular course with much lower concentration levels These experiments serve mainly to illustrate differences be-

TABLE V Lymph phosphol p ds before and af er nges on of cream (mg°o)

Ca e no	Fa ng	2 hrs	4 hrs	6 hrs	8 hrs	1? hrs	16 hrs
1	57	73	107	122	82	74	77
2	143	197	175	150	132	12	107
3	199	242	302	174			—
4	257	237	172	208	177	205	
5	218	187	266	252	104	125	52
Con rol	336	655	540	580	635	392	348
Con ol	301	535	505	675	510	488	234
Con ol	213	364	43?	208	177	141	125

TABLE VI Lymph choles erol bef re and after nges on of cream (mg o)

Case no	Fas ng	2 hrs	4 hrs	6 hrs	8 hrs	12 hrs	16 hrs
1	49	13	13	17	17	17	20
2	81	89	61	67	78	87	77
3	120	154	244	244			
4	80	78	86	94	91	94	—
5	96	90	172	75	103	103	120
Con ol	139	197	134	130	154	158	168
Con rol	106	126	109	109	85	95	106
C n rol	103	97	184	104	118	102	106

tween pat ents and control subjects in tl e lymphat c handl ng of the tracer s l stance and hardly allow of a quant ta ve eval at on of lymphat c ole c ac d transport as od ne is spl t off fa rly rap dly The i o ope concen rat on cur ves are l owe er very s m lar to those obta ned by total l p d analyses Fast ng level of 2—3 °o fat rose to peak values of 7 I fat wl le lymph l p d con centrat ons n pat ents were mucl lower and tl e al mentary respon e to fat feed ng correspond ngly small and irregular It appears tl at lympl phospl ol p d con cen rat ons normally are h gher than lymph cl olesterol (tables V and VI) and that lymph phosphol p ds normally par t cipate in the al mentary response to fat feed ng while lymph cholesterol does not increase regularly after fat ingest on

The cumultative lymphat c transport of neutral fat s recorded in f g 5 which shows rather w de var at ons but in con trast to lymph prote n transport values obta ned i the pat ents were all ins de tl e range of those of the control subjects again except for case 1 Tl e outcome of tl ese fat transport stud es s cons stent with the presence of m ld steatorrhoea of up to 20 g per day in case 1 wh le none of the rema n ng pat ents sl owed ev dence of impa red fat absorpt on

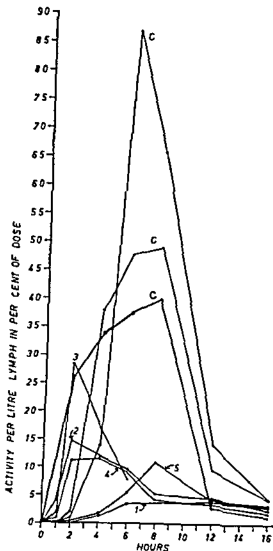


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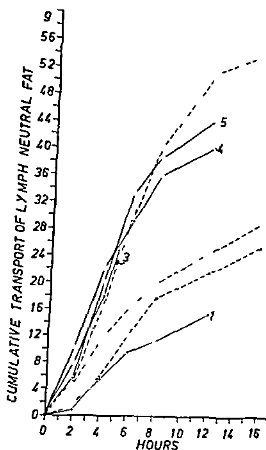


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TABLE V Lymph phospholipids before and after ingestion of cream (mg%)

Case no	Fasting	2 hrs	4 hrs	6 hrs	8 hrs	12 hrs	16 hrs
1	57	73	107	122	82	74	77
2	143	197	175	150	132	125	107
3	199	242	302	174	—	—	—
4	257	237	172	208	177	205	—
5	218	187	266	252	104	125	52
Control	336	655	540	580	635	392	348
Control	301	535	505	625	510	488	234
Control	213	364	432	208	177	141	125

TABLE VI Lymph cholesterol before and after ingestion of cream (mg%)

Case no	Fasting	2 hrs	4 hrs	6 hrs	8 hrs	12 hrs	16 hrs
1	29	13	13	17	17	17	20
2	81	89	61	67	78	87	77
3	120	154	244	244	—	—	—
4	80	78	86	94	91	94	—
5	96	90	172	75	103	103	[illegible]
Control	133	197	134	130	154	158	168
Control	106	126	109	109	[illegible]	[illegible]	106
Control	103	97	184	104	118	102	106

tween patients and control subjects in the lymphatic handling of the tracer substance and hardly allow of a quantitative evaluation of lymphatic oleic acid transport as iodine is split off fairly rapidly The isotope concentration curves are however very similar to those obtained by total lipid analyses Fasting levels of 2—3 % fat rose to peak values of 7—8 % fat while lymph lipid concentrations in patients were much lower and the alimentary response to fat feeding correspondingly small and irregular It appears that lymph phospholipid concentrations normally are higher than lymph cholesterol (tables V and VI) and that lymph phospholipids normally participate in the alimentary response to fat feeding while lymph cholesterol does not increase regularly after fat ingestion

The cumulative lymphatic transport of neutral fat is recorded in fig 5 which shows rather wide variations, but in contrast to lymph protein transport values obtained in the patients were all inside the range of those of the control subjects, again except for case 1 The outcome of these fat transport studies is consistent with the presence of mild steatorrhoea of up to 20 g per day in case 1 while none of the remaining patients showed evidence of impaired fat absorption

Discussion

The *main feature regarding* thoracic duct lymph in cases of constrictive pericarditis is a *greatly increased hydrostatic* pressure in the duct itself, and presumably in the hepatic and intestinal lymphatic vessels drained by the thoracic duct An increased flow of duct lymph under a high pressure was also observed in dogs with experimental constrictive pericarditis produced by obliteration of the pericardial cavity (2, 9) The underlying mechanism responsible for the high lymph pressure would then involve a sequence of decreased cardiac distensibility with inflow stasis, and rising hydrostatic pressure in the inferior vena cava and the portal vein *Starling (17) demonstrated that* obstruction of either of these great veins was *followed by increased flow rates of* duct lymph, and assumed that in these situations bulk filtration of fluid across the capillary wall, normally balanced by the opposing forces of hydrostatic and oncotic pressures, increases by virtue of a rising hydrostatic pressure in veins and capillaries

In normal tissues filtered fluid not offset by reabsorption through the capillary wall is removed by the lymphatics, and any *increase of filtration rate* by venous obstruction (8 17) will lead *to increased formation of lymph* Besides removing excess fluid, the lymphatic circulation also serves to remove protein, which escapes from all capillaries, and to return this extravascular protein to the blood stream via the thoracic duct Measurements of flow rates and protein content in lymph from several regions in dogs showed that this protein leakage occurs to a much greater extent in the liver and intestinal canal than in lymph from chest and limbs (19) *Estimates of the daily* extravascular circulation of protein returned by thoracic duct *lymph ranges from 50 % of total plasma* protein in dogs to 84 % in cats (19) Assuming a *normal average value of 2 g* albumin per kg body weight, the control subjects in the present study carried 29 %, 46 % and 52 % of their plasma albumin by the duct lymph One patient (case 3) without intestinal albumin loss returned 113 % of his plasma albumin, and two patients (cases 1 and 4) with albumin loss transported 100 % and 148 % of their plasma albumin pool calculated on a 24 hour basis *It should be emphasized that these figures serve only* for comparative purposes, being derived *from flow rates in cannulated ducts,* which may be different from those in the closed lymphatic system

Thoracic-duct lymph analyses show that all plasma protein fractions escape from the blood capillaries, although the smaller albumin molecules probably escape more readily than globulins, as suggested by somewhat higher lymph plasma ratios for albumin *It seems* obvious, however, that protein leakage is *determined by factors other than* concentration, molecular size and capillary pore dimensions. Analyses of lymph and plasma protein concentrations from different regions show that lymph protein concentrations are high in areas where hydrostatic capillary pressure is low (17, 18), which means that effective oncotic pressure increases with increasing hydrostatic pressure *The low lymph protein* concentrations in patients with constric-

TABLE VII Blood lymphocytes in patients with constrictive pericarditis

	Case no						Normal range
	1	2	3	4	5	6	
% of WBC	15	10	27	16	12	22	25–33
Lymphocytes/µl	900	850	1 620	620	750	840	1 500–3 000

tive pericarditis are consistent with this general principle

The experimental conditions applied in these studies do not permit delineation of the relative proportions of extravascular albumin which are lost into the intestinal lumen and those returned by duct lymph to the blood stream The lymphatic albumin transport in the patients suggests that extravascular protein transport is considerably increased in constrictive pericarditis In case 1 in whom lymphatic albumin transport was low, the extravascular transport was also increased relative to his intravascular albumin pool From these data on albumin transport it appears that the mechanism leading to intestinal albumin loss does not include any prevention by lymphatic obstruction of entry of duct lymph into the venous blood It is also obvious that there was still good lymphatic transport of fat except in case 1 as indicated by normal cumulative transport of neutral fat and absence of steatorrhoea

The high pressure system in the thoracic duct with its tributaries is then created not by any blocking of chylous transport but rather by increased formation of lymph due to high venous pressure In this situation intestinal albumin loss could be explained by increased leakage from intestinal lymphatic capillaries The albumin lost in this way must be replaced by newly synthesized albumin in the liver which can increase production only slightly, while the fat lost to the intestinal lumen is readily reabsorbed and resynthesized in the intestinal mucosa It is conceivable that such a condition is fully reversible when the cardiac constriction is relieved, as actually demonstrated (6) in three cases of constrictive pericarditis with intestinal albumin loss, and in one patient (7) who recovered from intestinal albumin loss as well as from steatorrhoea

It is consistent with this concept of lymph leakage that lymphopenia due to intestinal loss of lymphocytes has been demonstrated with a high frequency in clinical conditions with protein losing enteropathy (13) as well as in lymphatic hypertension experimentally produced by ligation of the thoracic duct (19) In the present series of patients lymphopenia was present in all cases (in a previous report (16) it was erroneously stated that the blood differential count in case no 1 was normal) except one (table VII)

It would be expected that persistence of lymphatic hypertension over a period of several years might eventually lead to anatomical lesions including intestinal

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It would be expected that persistence of lymphatic hypertension over a period of several years might eventually lead to anatomical lesions including intestinal

lymphangiectasia as occurred in our case 1 When such lesions are present, increased quantities of lymph may escape by rupture of dilated lymphatics, thereby establishing a fat- and protein-losing enteropathy

Summary

Albumin turnover and thoracic-duct lymph flow were studied in six cases of constrictive pericarditis and in three control subjec s Intestinal loss and a high fractional turnover rate were found in three patients with hypoalbuminaemia

Greatly increased flow rates under *high pressures were demonstrated in all* the patients Evaluation of fat transport after oral administration of labelled oleic acid and a high fat meal revealed a normal fat transport capacity in all cases except in one patient with steatorrhoea Extravascular protein transport was increased in all patients including those with intestinal albumin loss

It is concluded that the abnormal features of albumin turnover are due *to* increased formation of lymph in the liver and intestinal tract, caused by increased hydrostatic venous pressure Lymphatic hypertension is probably responsible for leakage of lymph leading to irreversible intestinal loss of protein and of lymphocytes, while fat may be reabsorbed *If the high-pressure system* prevails for a long time, however, structural lesions may develop, including lymphangiectasia, oedema end adhesions

Acknowledgements

We should like to express our appreciation to Dr C B Madsen for permission to carry out isotope work in the Radiophysics Laboratory We are indebted to Dr H Gotzsche for the opportunity to study two patients under his care in the Department of Cardiology Miss Jytte Sorensen provided careful technical assistance

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The Occurrence of Benign, Essential Monoclonal (M Type), Non-macromolecular Hyperglobulinemia and its Differential Diagnosis

IV Studies in the Gammapathies

By

Jan Waldenström

In 1955 a programme was initiated for the collection of sera from patients showing hypergammaglobulinemia with narrow bands (essential monoclonal according to the author's nomenclature, 1961) Since then C B Laurell and the author have found numerous patients who did not develop any signs indicating multiple myeloma in spite of their typical monoclonal electropherograms Some of these patients' histories have already been discussed briefly in a previous paper (8) and the detailed protein analyses for the majority of the cases may be found in a report by Heremans (5) (the numbers before the patients' initials in this paper are the same as in that publication)

A large number of patients (> 100) has now been followed for more than one year The material is being treated as a whole by Hallen and the present paper only gives data on some of the patients who have been followed closely over a period of *more than* $2^1/_2$ *years* or have negative post mortem findings Those patients with an increase in macroglobulins will be treated in a special *paper on* this subject (19) All the patients discussed in the present paper come from Malmö

In 1944 1952 — and in 1957 — I first described and then extended our views on what I had called essential hyperglobulinemia In a review from 1952 I wrote in the section entitled Essential hyperglobulinemia 'In *view of the* favourable prognosis it is important *that* this condition be recognized In the absence of a better designation I have chosen to call it essential hyperglobulinemia This syndrome should *not be confused* with myeloma The histories of two patients, who had had a continuously increasing erythrocyte sedimentation rate (ESR) since 1945 or 1946, and who had

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been followed until 1951 without developing clinical signs of myeloma, were presented Figures were produced showing the narrow high peak in the β or γ regions of the myeloma type In my chapter in Thannhauser's Textbook (17) the occurrence of essential hypergammaglobulinemia with narrow and with broad bands is also discussed

Interesting observations on the same type of patient have been published by several authors in the last years They will be reviewed only briefly in the following pages, and the reader is referred to the original publications

The most extensive paper was published by Osserman in 1958 (12) A large number of observations on persons who had narrow bands without showing signs of myeloma was described, and the possibility of real myeloma in some of the cases was discussed The sera were not examined for the presence of macroglobulins In the following year, Owen et al (13) observed ten patients with M components Three of them definitely had macroglobulins, one questionably had a macroglobulin, and four had 7 S components, another probably had a γ_{1A} component No ultracentrifugation was carried out on one serum Five patients had evidence of reticuloendothelial disease and one had thyroid carcinoma It is surprising that so few patients have had premyeloma or essential benign hyperglobulinemia Case 1 (7 S), however, died and had no myeloma In the same year, Hammack et al (4) published the same type of observation under the name dysgammaglobulinemia syndrome One of their patients showed a macroglobulin, while the others had 7 S components The period of observation in one case was 3½ years Ogryzlo et al (10) from Canada published their experiences with a few patients having M components who had no typical disease that could account for this change Ultracentrifugation was not performed and it is therefore difficult to tell how many patients could have been suffering from macroglobulinemia Fudenberg and Kunkel (3) and Christenson et al (2) have observed M components in patients with hemolytic anemias connected with high titres of cold agglutinins In some instances it was shown that the M component could be removed by repeated agglutination with red cells These instances all represent increases in macroglobulin treated in another paper (19) During the last two years several similar observations have been made for instance by Wewalka in Vienna and by Wuhrmann in Winterthur It is, therefore, obvious that such conditions occur in Sweden, U S A, Canada, England, Australia, Switzerland and Austria Our experience from this country indicates that the condition is by no means rare (about 3 % in a population > 70 years of age (6))

In the following I have tried to arrange the case histories into more or less natural groups It must be pointed out, however, that this is practically complete terra incognita and therefore the ideas of today may have to be, and have often been, revised tomorrow The groupings should, therefore, be regarded as purely temporary and tentative They are, 1) patients whose electrophoretic picture might indicate myeloma, but in whom the post mortem was negative, 2) pa-

tients with clearcut myeloma, possibly preceded by premyeloma , 3) patients having cancer with benign hyperglobulinemia or myeloma and 4) patients with a very long period of clinical observation and high γ globulin values without signs of multiple myeloma Group 4 will be followed up by Hallen

1 Patients with suspected myeloma clinically but negative autopsy findings

Some patients with monoclonal type globulins must be discussed in some detail because it would seem possible that they had developed myeloma, even if the post mortem gave no indications of the diagnosis A M, O H, A L, J N, O L and perhaps S M belong to this group

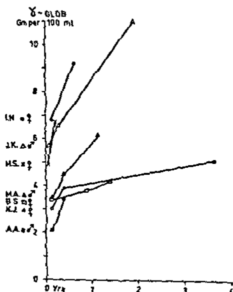


Fig 1 Seven cases of myeloma The very rapid increase in M-component is clearly seen

165 A M Woman born in 1883 In April 1956 she had early symptoms of Parkinson s disease On Oct 12 1957 the patient suffered a leftsided hemiplegia She now had sign of very severe Parkinson s disease Her ESR was much increased 60—80 mm A serum electrophoresis was performed and revealed a marked increase in α_2 and a sharp narrow band in the γ region (1 5 %) The serum albumin was 2 8 % No ultracentrifugation was done Her normal γ fraction was low the pathological β globulin passed into the urine Sternal puncture showed 4 0 % plasma cells There was no roentgenological examination of her skeleton The patient died on Jan 13 1958 The marrow in several vertebral bodies and in the femur was found to be normal Some small groups of plasma cells were present that looked completely normal and there were no signs indicating myeloma Her blood values were determined immediately before death Hb 84 % R B C 4 0 mill W B C 6200 and ESR 78 mm

The fact that a pathological monoclonal globulin was present in the urine might possibly be regarded as an argument in favour of myeloma

This case history raises the question of whether it is possible to exclude the presence of multiple myeloma at the post mortem I regard these findings by a competent pathologist, when the clinician has expressed the suspicion of multiple myeloma, as almost convincing proof that this patient had a narrow band without suffering from myeloma

Another pat ent of the same kind was

155 O H Woman born in 1883 She was admitted in Aug 1957 for weight loss and tiredness Sternal puncture showed 4 8 % plasma cells Roentgenological examination of the skeleton revealed a suspicion of osteolytic foci in the right scapula and in some of the ribs on the right side Changes were also noted in the calvarium that might possibly indicate early myeloma The patient had a normochromic anemia of 57 % with 2 6 mill R B C. W B C and platelets were normal After one month in the hospital the patient suddenly died from a pulmonary embolism Her bone marrow was examined carefully and some

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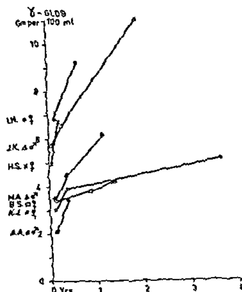


Fig 1 Seven cases of myeloma The very rapid increase in M component is clearly seen

175 A M Woman born in 1883 In April 1956 she had early symptoms of Parkinson's disease On Oct 12 1957, the patient suffered a leftsided hemiplegia She now had signs of very severe Parkinson's disease Her ESR was much increased 60—80 mm A serum electrophoresis was performed and revealed a marked increase in α_2 and a sharp narrow band in the γ region (1 5 %) The serum albumin was 2 8 % No ultracentrifugation was done Her normal γ fraction was low the pathological β globulin passed into the urine Sternal puncture showed 4 0 % plasma cells There was no roentgenological examination of her skeleton The patient died on Jan 13 1958 The marrow in several vertebral bodies and in the femur was found to be normal Some small groups of plasma cells were present that looked completely normal and there were no signs indicating myeloma Her blood values were determined immediately before death Hb 84 %, R B C 4 0 mill W B C 6200 and ESR 78 mm

The fact that a pathological monoclonal globulin was present in the urine might possibly be regarded as an argument in favour of myeloma

This case history raises the question of whether it is possible to exclude the presence of multiple myeloma at the post mortem I regard these findings by a competent pathologist when the clinician has expressed the suspicion of multiple myeloma, as almost convincing proof that this patient had a narrow band without suffering from myeloma

Another patient of the same kind was

155 O H Woman born in 1883 She was admitted in Aug 1957 for weight loss and tiredness Sternal puncture showed 4 8 % plasma cells Roentgenological examination of the skeleton revealed a suspicion of osteolytic foci in the right scapula and in some of the ribs on the right side Changes were also noted in the calvarium that might possibly indicate early myeloma The patient had a normochromic anemia of 57 % with 2 6 mill R B C W B C and platelets were normal After one month in the hospital the patient suddenly died from a pulmonary embolism Her bone marrow was examined carefully and some

sections from the vertebral bodies contained a slight increase in plasma cells that were never aggregated in tumourlike infiltrations The ribs femur and calvarium were examined, and no evidence of myelomatosis was found There were no other findings of special interest at the post mortem This patient had on electrophoresis *a strong β band (2 4 %) with a low normal γ globulin* The hexose content was low

This patient's history is obviously of the same type as in the previous case, 165 A M, even if the clinical signs of myeloma seemed to be more definite with marked anemia and suspicious skeletal foci The following patients may belong to the same group, although the most probable diagnosis seems to be essential benign hypergammaglobulinemia

161 A L Woman born in 1874 She was *admitted to the Hospital for Chronic Diseases* in 1958 with severe cardiac decompensation She had a slight anemia with 3 9 mill R B C, and an ESR of 12 mm Examination of the serum revealed a small γ type band with very *slow migration (33 % 7 S γss)* Sternal puncture and roentgenological examination of the bones were not performed At the post mortem only sections from the femoral marrow were examined and these were normal without signs of myeloma The clinical and anatomical data on this patient are too sparse to allow valid conclusions

395 J N Man born in 1882 He had had chronic bronchitis since *1950* He was admitted in March 1960 in a cachectic state Hypo*albuminemia* with a narrow γ band was demonstrated A biopsy from the iliac crest showed collections of plasma cells that could have represented myeloma but were not convincing proof of the diagnosis Roentgenological examination of the spine and thorax showed no signs of myeloma but a few rounded foci that could represent early myeloma were noted in the skull There was no anemia, although a mild leucopenia was *noted* The patient was readmitted in May 1961 with signs of cardiac decompensation A repeat electrophoresis revealed a band of 0 9 %, and a background γ of 0 8 % The total γ was *1 7 % at this time and had been 1 9 %* on the previous occasion This probably means that his condition had not changed The Hb was 90 %, R B C 4 6 mill, W B C 4000 NPN 35 mg/100 ml There was no proteinuria The patient s skull was re examined and a few small rounded foci were noted, which were probably *of no significance* The twelfth thoracic vertebra was compressed and cuneiform The patient died on April 5, 1962, of increasing decompensation The post mortem showed purulent bronchitis with wide *spread pneumonic infiltrations and signs of* vascular sclerosis Microscopically no signs of typical myeloma were present in the vertebral bodies Plasma cells were numerous with an even distribution and did not show any foci *Plasma cells* were also present in increased numbers in the lymph glands and spleen, but were never collected in foci It is interesting that this patient had a border line value for rheumatoid factor and an achryl plast fixation of I 160 (strongly positive), but no antigamma globulin It is, of course impossible to tell *if this patient* had an early diffuse myeloma or merely an increase in plasma cells from some other cause

The following patient might seem to be a typical example of the development of myeloma followed from the beginning The post mortem disclosed no evidence of myeloma, however

O L Man born in 1887 About 1954 he developed symptoms of diabetes and in March 1957 was admitted for syncope Hematological examination at this time revealed *R B C 6 0 mill, Hb 105 %*, W B C 8900, platelets 250,000 and ESR of 4 mm The differential count was normal The serum cholesterol was 448—331 mg/100 ml The spleen was not palpable Nothing was done

for his polycythemia and his diabetes was quite benign He was readmitted in April 1960 for signs of osteoporosis with low back pain An anemia with 3 mill R B C and 11 g% Hb was found A differential count showed some neutrophilic myelocytes and plasma cells with a W B C of 6 000—7 000 and a normal platelet count The basophilic cells were on the high side but otherwise there were no signs indicative of leukemia The spleen was not palpable Roentgenological examination of the skeleton seemed to show destruction of the twelfth thoracic vertebra and also a destructive focus in the twelfth rib The skull was normal A sternal puncture revealed no increase in plasma cells X rays of the stomach showed nothing pathological Intravenous pyelogram could not be done because of the severe back pains Serology was completely negative Serum electrophoresis in March 1957 was considered to be unremarkable but upon re-examination in 1960 a narrow rapid γ band was just perceptible This indicates that the patient had a very slight increase in one γ fraction as early as 1957 (See fig 2 in Waldenstrom (18))

The development of the electrophoretic picture is demonstrated below

The patient was treated with X ray therapy to his twelfth thoracic vertebra and seemed to improve The most remarkable feature in this connection is the peak of monoclonal γ globulin present in Sept 1960 that later showed signs of regression Could this be the result of successful treatment of a solitary myeloma in the twelfth thoracic vertebra?

The patient returned for follow up examination and had few complaints referable to his back but was not able to blow his trumpet in the orchestra After July 1961 psychic troubles with some aphasia and depression were evident On July 17th a left sided hemiplegia occurred followed by death within a few days His diabetes seemed to have been well controlled without insulin The autopsy showed xanthoma in the left achilles tendon generalised arteriosclerosis (aorta) thrombosis arteriae subclaviae sin and multiple encephalomalaciae bilaterally in the basal ganglia The compression fracture showed no signs of myeloma

This case history points to the interesting fact that not even a combination of monoclonal hyperglobulinemia and compression fracture of a vertebra is enough to make the diagnosis of myeloma!

In my opinion the following patient may possibly have had real myeloma even though the clinical examination could not be very complete and there was no post mortem

S M Woman born in 1884 Heredity O No previous illness known In Nov 1957 the patient complained of fatigue and lost 7—8 kg in weight She suffered from Parkinson s disease The first *electrophoresis done on* Jan 11 1958 revealed an albumin of 3 8 % and a slight increase in β_2 with a passage of this fraction into the urine The next electrophoresis done on June 19 1958 showed an albumin of 4 1 % β_2 0 4 % and γ 0 6 % In Sept 1958 the β_2 was 0 4 % the γ 0 5 % A peculiar shape of the β fraction was noted The last examination on Jan 15 1960 revealed an albumin of 4 1 % β_2 0 52 % (rather

		Alb	α	α	β	β	γ
March	1957	4 2	0 3	0 6	0 4	0 3	0 8 (faint band)
Sep	1960	4 6	0 3	0 5	0 5	0 3	1 6 + 0 ?
Nov	1960	3 6	0 3	0 6	0 4	0 34	1 3 + 0 5
Dec	1960	4 0	0 3	0 8	0 5	0 4	1 1 + 0 4
June	1961	4 39	0 3	0 7	0 5	0 4	0 6 + 0 3
July	1961	5 1	0 3	0 7	0 6	0 4	0 7 + 0 3

sections from the vertebral bodies contained a slight increase in plasma cells that were never aggregated in tumourlike infiltrations The ribs, femur and calvarium were examined, and no evidence of myelomatosis was found There were no other findings of special interest at the post mortem *This patient had on* electrophoresis *a strong β_2 band (2 4 %) with a low normal γ globulin* The hexose content was low

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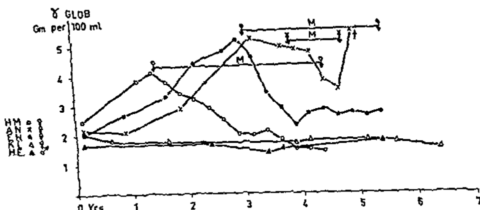


Fig 2 Three cases of slowly developing myeloma The 3 upper curves show rap d ncrease in M component w th reversal on Melphalan treatment The 2 lower essent al monoclonal

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2 The follou ng three pat ents have had slouly develop ng myeloma (fig 2)

H M Woman born n 1875 Her prev ous h story is of no mportance except for repeated thromboses n 1945 1947 and 1953 In July 1959 she developed pa ns in the right leg caused by a thrombosis She was sl ghtly ane m c Serum electrophoresis showed an n crease n γ_2 and an albumin of 3 9 % A skeletal survey on July 14 1959 revealed some ery inconsp cuo is foci n the cran um? but o he wise nothing patholog cal She v as n excellent general cond t on but after a fe v days developed hematemesis She was treated w h transfus ons with good result A sternal puncture showed a rather h gh plasma cell con ent 6 8 % There was no prote nuria and the serum calcium as normal The ESR was 40—60 mm The pat ent was read m tted n Nov 1960 Roentgenolog cal ex am na on of the skeleton re ealed no certa n des ruction The development of her cond t on may be seen in the graphs wh ch sho v a steady increase n γ globul n before treat ment

This pat ent has a h gh t tre of thyro d anti bod es very low B_{12} alues and a Schill ng test of 7 % absorpt on of B Her anem a was treated in a paper by Larsson (7) It seems almost certa n that th s is an instance of mye loma even thou h the h gh t tre of thyro d ant bod es is an unusual find ng The pro- gressi e increase in patholog cal globul ns fa vours this assumpt on The pat ent s anem a d d not respond to the B_{12} in the S hill ng test In Sept 1959 the plasma cell count was 6 6 % She is now on Melphalan treatment her γ globul n having decreased cons derably (from 3 9 % to < 2 %) after two years treat ment The last roentgenolog cal exam nation of the osseous system d d not reveal any cer ta n osteolysis The last sternal puncture was performed n December 1962 showing 3 5 % plasma cells

19C 4 N Woman born in 1906 Her pre vious history is not of special interest except ing fever and joint pa ns n 1941 and symp- toms of rheumato d arthr tis in 1946 Her ESR was above 60 S nce then she has had various symptoms and her ESR has been between 30 and 40 mm In 1948 1951 and 1953 she had pneumonia In 1956 and 1957 she had com plaints referable to the abdomen wh ch were regarded as be ng due to divert culitis The ESR in 1957 was 49 mm and an abnormal narrow γ band of 2 0 % was present In Sept she had pneumon a On June 11 1958 she was adm tted to the Medical Cl n c w th a

broad), and γ 0 5 % The combination of a broad β, low γ and passage of β into the urine was thought to indicate a protein disturbance of myeloma type A skeletal survey was negative The patient died at home on June 11, 1960 No post mortem was obtained She had no proteinuria at the last examinations

8 A S Woman born in 1891 In 1954 she complained of 'troubles with the kidneys' In 1955 she suffered fever and loss of weight with increased ESR (50—115 mm) and anemia Electrophoresis was done at this time and showed *a narrow γ band* Roentgenological examination of the skeleton was negative In May 1955 no signs of any definite disease were found, since then she has had a consistently high ESR

Re-examination in 1956, 1957 and 1958 did not reveal any definite signs of disease, but the patient had varying subjective symptoms *referable to different organs A sternal puncture* revealed a plasma cell content of 6 % on one occasion, and 1 5 % on another The γ fraction was 2 8 % (γss) on several occasions but no signs of myeloma were found on roentgenological examination She had a leukopenia of 1,300 W B C On this occasion the rheumatoid factor titre was quite high *(1/1024)*

The patient was readmitted in Nov 1959 for observation At this time she still had *leukopenia of 1,400—2,200 W B C, and a* normal differential count Rose Waaler *1/128* Achryl fixation *1/160* Antigamma positive

In Dec 1960 the patient had severe psychic disturbances and was admitted to a chronic hospital She complained of pains all over" There was tenderness over sternum and clavicles, otherwise physical examination was non contributory There was some anemia R B C 2 8 mill, Hb 11 g% W B C 2,500—3,900 The differential count was normal Platelets were *150,000 No proteinuria* and no azotemia were noted *Serum calcium* and phosphorus were normal BSP *retention* was 10 % at 30 *minutes* (normal) Skeletal survey revealed no sign of myeloma in the spine, pelvis, skull or thorax, and no signs of chronic arthritis in either hand *Sternal puncture* revealed 2 8 % plasma cells! Serological examination showed Rose Waaler test positive 1/64 Achryl fixation 1/160 Antigamma negative Because of the very obscure clinical picture, with polysymptomatic complaints, cautious treatment with Melphalan was started in Dec 1961 The patient then had a positive Rose Waaler test and achryl fixation 1/640 The Melphalan treatment had no obvious effect and the patient was again transferred to the Department of Chronic Diseases where she died on July 13th, 1963 The post mortem showed diffuse increase in plasma cells in the bone marrow (diffuse myeloma?), *enlarged lymph glands in different sites with* plasma cellular infiltrations in glands, liver, *spleen and kidneys She also had a steatosis* hepatis with early cirrhosis (fig 4)

This is, of course, a very interesting history of long duration without development of evident myeloma It should be noted that the very marked band with decreased back-ground γ globulin was *no longer visible as clearly as before*, as the patient had developed a polyclonal back ground γ globulin This is very rare but has been seen in a few patients with liver cirrhosis as a complication Skeletal roentgen had remained negative throughout

L L Man born in 1882 In 1939 he was operated on for an ulcer In 1957 he complained of abdominal trouble Serum electrophoresis showed a *narrow band in the β region* A skeletal survey was negative Sternal puncture revealed sparse, atypical *(plasma?)* cells Skeletal survey done in May 1961 was negative *The patient* was re examined in Oct 1961 He had no pains and no anemia and at that time the *serum electrophoresis* was as before A few days later he had a fractured *femoral neck* and was treated in the Orthopedic Clinic He died suddenly with copious melena from a big duodenal ulcer The post mortem also discussed general arterioscler-

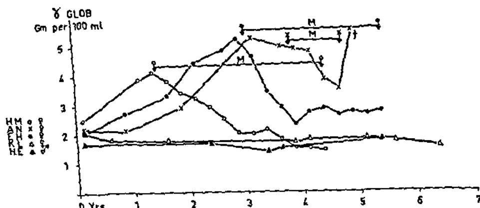


Fig 2 Three cases of slowly developing myeloma The 3 upper curves show rapid increase in M component with reversal on Melphalan treatment The 2 lower essential monoclonal

sis Numerous slides were taken from the bone marrow but no signs of myeloma were found and no other tumour infiltrations

2 The following three patients have had slowly developing myeloma (fig 2)

H M Woman born in 1875 Her previous history is of no importance except for repeated thromboses in 1945 1947 and 1953 In July 1959 she developed pains in the right leg caused by a thrombosis She was slightly anemic Serum electrophoresis showed an increase in γ_2 and an albumin of 3 9 % A skeletal survey on July 14 1959 revealed some very inconspicuous foci in the cranium? but otherwise nothing pathological She was in excellent general condition but after a few days developed hematemesis She was treated with transfusions with good result A sternal puncture showed a rather high plasma cell content (6 8 %) There was no proteinuria and the serum calcium was normal The ESR was 40—60 mm The patient was readmitted in Nov 1960 Roentgenological examination of the skeleton revealed no certain destruction The development of her condition may be seen in the graphs which show a steady increase in γ globulin before treatment

This patient has a high titre of thyroid antibodies very low B_{12} values and a Schilling test of 7 % absorption of B_{12} Her anemia was treated in a paper by Larsson (7) It seems almost certain that this is an instance of myeloma even though the high titre of thyroid antibodies is an unusual finding The progressive increase in pathological globulins favours this assumption The patient's anemia did not respond to the B_{12} in the Schilling test In Sept 1959 the plasma cell count was 6 6 % She is now on Melphalan treatment her γ globulin having decreased considerably (from 3 9 % to 2 2 %) after two years treatment The last roentgenological examination of the osseous system did not reveal any certain osteolysis The last sternal puncture was performed in December 1962 showing 3 5 % plasma cells

196 A N Woman born in 1906 Her previous history is not of special interest except ing fever and joint pain in 1941 and symptoms of rheumatoid arthritis in 1946 Her ESR was above 60 Since then she has had various symptoms and her ESR has been between 30 and 40 mm In 1948 1951 and 1953 she had pneumonia In 1956 and 1957 she had complaints referable to the abdomen which were regarded as being due to diverticulitis The ESR in 1957 was 49 mm and an abnormal narrow γ band of 2 0 % was present In Sept she had pneumonia On June 11 1958 she was admitted to the Medical Clinic with a

polysymptomatic history Her blood pressure was 200/115 mm Hg Serum electrophoresis revealed a narrow γ band of 2 1 % and an albumin of 4 4 %, otherwise the findings were normal She had 10 % plasma cells and no L E cells Extensive serology was completely negative No anemia was demonstrated Her W B C was 6 200 The patient was readmitted in Feb 1960 and underwent resectio coli for her diverticulitis No cancer was found She still complained of fleeting pains in her joints Physical examination disclosed some hypertension (190/120) She had a marked increase in plasma cells (18 %) Re-examination in March 1961 revealed no evidence of a progressive anemia, but a further increase in γ globulins was noted In Oct 1961 the patient was readmitted for Melphalan treatment This treatment had some effect but had to be stopped because of increasing leukopenia and thrombocytopenia In Sept 1962 she had a big palpable abdominal tumour and died on Dec 7th 1962 She had myelomatosis of the bone marrow large plasma-cellular infiltrates in the kidneys and large malignant infiltrations with atypical plasma cells retroperitoneally

It is interesting to note that the plasma globulins did not show a steady rise initially, but remained constant for a year, as in benign hypergammaglobulinemia and then started to increase as in myeloma (fig 2) The patient was under observation for only one year during this initial stage

The patient's sister M J born in 1914, suffers from typical S L E with a false positive Wasserman and a marked polyclonal hypergammaglobulinemia Data for the two sister's electrophoretic diagrams are given in Waldenstrom (17) Doctor Leonhardt has investigated all our patients with S L E genetically and this is a rare example of monoclonal hyperglobulinemia in an S L E family

131 M C Woman born in 1887 Her previous history is of no special interest. The patient suffered from a severe depression in 1954 Her ESR was then 14 mm In April 1957 her ESR was found to be 50 mm and a pathological electrophoretic fraction was found (γ 3 0 %) Her plasma cell count was 4 4 % In Oct. 1957 her ESR was about 100 mm with a γ (7 S γss) globulin of 4.2 % Her sternal marrow contained 2 % plasma cells The patient has been re-examined several times In June 1959 she still had a severe depression and some anemia but her ESR had decreased to 40 mm and her skull showed no signs of myeloma The patient was re-examined in Sept 1961 Hb 68 % R B C 3 2 mill W B C 3 100 ESR 46 mm and thrombocytes 208 000 The cranium revealed no signs of myeloma Serum electrophoresis showed 4 0 % γ and 5 0 % albumin Extensive serology was negative The patient was admitted to the Medical Clinic in September 1962, severely depressed and very nervous Skeletal survey showed no myeloma Extensive serology was negative, but agglutination of erythrocytes coated with thyroglobulin was positive 1/250 Blood values R B C 3 2 mill Hb 75 % W B C 1 700—2 600 normal platelets Electrophoresis showed some further increase in globulin but no proteinuria Sternal puncture showed 6 4 % plasma cells The patient was readmitted in September 1963 very depressed No typical bone pains typical foci have developed in the skull but in no other bones W B C 2 000—4 000 Platelets normal R B C 2 5 mill Plasma cells in sternal marrow 11 4 % The patient was put on a short course of Melphalan with no obvious effect (see fig 3 upper curve)

226 E H Woman born in 1903 The patient has a long history including cholelithiasis uretherolithiasis pains in the knees etc In Feb 1958 electrophoresis showed a low normal γ globulin and a β_2 of 2 1 % A skeletal survey was negative She was first admitted to the Medical Clinic on Feb 15 1960 A sternal puncture disclosed an increase in plasma cells In May 1960 the patient complained of pains in her back and a compres-

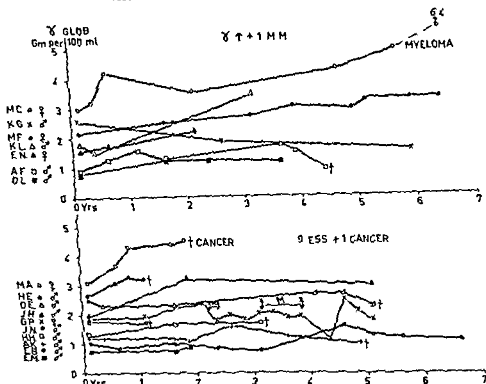


Fig 3 Six cases of essential benign monoclonal The remarkable constancy of the M-component is clearly seen

sion fracture of the ninth thoracic vertebra was noted No focal signs were evident Her skull was normal The diagnosis of myeloma was regarded as somewhat uncertain The patient later developed pains in the thorax and it seemed advisable to start Melphalan treatment She was re-examined roentgenologically in Oct 1960 and it was thought that she had myelomatous foci in the cranium the costae and the vertebrae with compression fractures from the ninth thoracic vertebra down to the first lumbar vertebra Her pathological globulin had increased Her body length had decreased from her normal 151 cm to 144.5 cm Melphalan therapy was started in Dec 1960 with excellent results on both the serum proteins and her general condition She was able to work full time again (18)

It is of course impossible to tell when myeloma ' really started in these four patients H M , A N M C , and E H , but it is clear that there was *an initial* stage with uncharacteristic symptoms (*fig* 2)

3 Cancer with myeloma or benign essential hypergammaglobulinemia

The following patient showed a possible connection between carcinoma and a monoclonal increase in γ_{SS} or γ_{1A} globulin (but no myeloma) as was discussed by the author in 1961 (17)

278 M A Woman born in 1893 She had a cholecystectomy in 1948 and suffered from

polysymptomatic history Her blood pressure was 200/115 mm Hg Serum electrophoresis revealed a narrow γ band of 2 1 % and an albumin of 4 4 %, otherwise, the findings were normal She had 10 % plasma cells and no L E cells Extensive serology was completely negative No anemia was demonstrated Her W B C was 6,200 The patient was readmitted in Feb 1960 and underwent resectio coli for her diverticulitis No cancer was found She still complained of fleeting pains in her joints Physical examination disclosed some hypertension (190/120) She had *a marked increase in plasma cells (18 %)* Re-examination in March 1961 revealed no evidence of a progressive anemia, but a further increase in γ globulins was noted In Oct 1961 the patient was readmitted for Melphalan treatment This treatment had some effect but had to be stopped because of increasing leukopenia and thrombocytopenia In Sept 1962 she had a big palpable abdominal tumour and died on Dec 7th, 1962 She had myelomatosis of the bone marrow, large *plasma cellular infiltrates in the kidneys* and large malignant infiltrations with atypical plasma cells retroperitoneally

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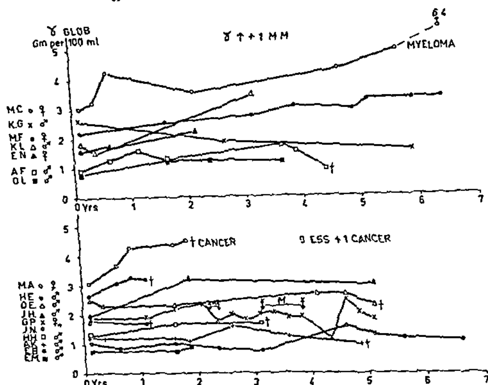


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It is interesting to note that the plasma globulins did not show a steady rise initially, but remained constant for a year, as in benign hypergammaglobulinemia, and then started to increase, as in myeloma (fig 2) The patient was under observation for only one year during this initial stage

The patient's sister *M J* born in 1914, suffers from typical S L E, with a false positive Wasserman and a marked polyclonal hypergammaglobulinemia Data for the two sister s electrophoretic diagrams are given in Waldenstrom (17) Doctor Leonhardt has investigated all our patients with S L E genetically, and this is a rare example of monoclonal hyperglobulinemia in an S L E family

131 M C Woman born in 1887 Her previous history is of no special interest The patient suffered from a severe depression in 1954 Her ESR was then 14 mm In April 1957 her ESR was found to be 50 mm and a pathological electrophoretic fraction was found (γ 3 0 %) Her plasma cell count was 4 4 % In Oct. 1957 her ESR was about 100 mm with a γ (7 S γ_{2ss}) globulin of 4 2 % Her sternal marrow contained 2 % plasma cells The patient has been re examined several times In June 1959 she still had a severe depression and some anemia, but her ESR had decreased to 40 mm and her skull showed no signs of myeloma The patient was reexamined in Sept 1961 Hb 68 %, R B C 3 2 mill, W B C 3,100, ESR 46 mm and thrombocytes 208,000 The cranium revealed no signs of myeloma Serum electrophoresis showed 4 0 % γ and 5 0 % albumin Extensive serology was negative The patient was admitted to the Medical Clinic in September 1962, severely depressed and very nervous Skeletal survey showed no myeloma Extensive serology was negative, but agglutination of erythrocytes coated with thyroglobulin was positive 1/250 Blood values R B C 3 2 mill, Hb 75 %, W B C 1,700—2,600, normal platelets Electrophoresis showed some further increase in globulin but no proteinuria Sternal puncture showed 6 4 % plasma cells The patient was readmitted in September 1963, very depressed No typical bone pains, typical foci have developed in the skull but in no other bones W B C 2 000—4,000 Platelets normal R B C 2 5 mill Plasma cells in sternal marrow 11 4 % The patient was put on a short course of Melphalan with no obvious effect (see fig 3 upper curve)

226 E H Woman born in 1903 The patient has a long history, including cholelithiasis uretherolithiasis, pains in the knees, etc In Feb 1958 electrophoresis showed a low normal γ globulin and a β_2 of 2 1 % A skeletal survey was negative She was first admitted to the Medical Clinic on Feb 15 1960 A sternal puncture disclosed in increase in plasma cells In May 1960 the patient complained of pains in her back and a compres-

360 A R Woman born in 1882 There was a previous history of cardiac decompensation (auricular fibrillation) In Dec 1958 the patient had a *respiratory infection* In Oct 1959 an abnormal β_2 component was noted and a skeletal survey revealed a suspicion of small osteolytic foci A sternal puncture in Nov 1959 showed about 10 % plasma cells Re examination of skeletal roentgenograms could not confirm the suspicion of myeloma In June 1960 the patient was practically free from dyspnea and had a low fibrillation on continuous digitalis therapy There was no anemia A slight proteinuria was noted Her ESR was 57 mm A narrow band resembling the normal β_2 fraction was present in a concentration of 0 7 % and later increased to 0 9 % The globulin was a β_{2A} (γ_{1A})

In Dec 1961 the patient noticed a swelling on the right leg A biopsy was performed and a subcutaneous tumour was noted which did not infiltrate the skin but adhered to the muscles The histological diagnosis was *fibroliposarcoma* After the operation the patient developed massive gastrointestinal bleeding and died in shock The post mortem showed enteritis gravis with hemorrhagic necrosis in the jejuno-ileum and colon and also a massive infiltration with leukocytes The bone marrow in the femur contained rather numerous diffuse or clustered plasma cells of normal appearance These changes were not clearcut enough to allow a definite diagnosis of myeloma

423 A S Man born in 1871 His previous history is unimportant In May 1960 he developed a severe cough with fever and had associated weight loss He was admitted to the Hospital for Infectious Diseases on June 18 1960 with right sided lower pneumonia that responded well to chemotherapy *The patient had a carcinoma of the skin on the left cheek* and radiological treatment was therefore initiated An extensive serological evaluation showed a positi e achryl plast I 320 A narrow γ (γ_{1A}) band was noted on two serum electrophoretic examinations There was neither anemia nor leukocytosis A skeletal survey showed no signs of myeloma

The following is another case history that remained completely enigmatic for several years The final stage was dominated by the development of a cancer

219 H H Man born in 1892 In Jan 1930 the patient developed swelling of the right knee and atrophy of the right leg In 1912 he had a sudden paresis of the left leg and a blood pressure of 190/110 There was excellent recovery after one month The condition was then regarded as ramollitio cerebri In 1944 his vision was suddenly impaired again with good recovery In 1950 the patient developed sudden amblyopia in the right eye with diplopia and transient glycosuria He was symptomfree in ten days In 1953 amblyopia occurred one morning with *vomiting* The patient was admitted with a right sided paresis nervi IV dx Blood pressure was normal Neurological examination was completely normal In 1954 as in 1937, he suffered an attack of syncope after *micturition* His neurological state was completely normal His blood pressure was 160/90 *Slight diabetes was noted* In June 1957 he had vertigo and vomiting followed by diplopia caused by a left sided external oculomotor palsy, with accompanying paresis of the right leg After some months complete recovery ensued In Nov 1957 there was renewed paresis in the right leg followed by paresis in the left leg with severe pains on the left side There was no diplopia He was admitted in Feb 1958 and could not stand firmly on his legs A definitely impaired sense of touch on the right lower leg was noted His pain and temperature senses were normal Patellar reflexes were absent bilaterally Lumbar puncture done twice at this time showed no increase in cells the total protein was 95 and 97 mg % and a narrow band in the serum γ globulin (7 S γ_{SS}) was seen *The same percentage of protein fractions was noted in the serum and the C S F* Roentgenological examination revealed no signs of myeloma the myelogram was normal Sternal puncture was normal (2 8 % plasma cells) There was gradual lessening of the severe pains in the left leg after several months Achilles reflexes were

"gallstones" in 1958 Later in 1958 she contracted bronchopneumonia Electrophoresis showed a strong narrow band (2 7 %) A sternal puncture revealed 5 6 % plasma cells The patient had an anemia with 60 % Hb and 3 3 mill R B C The patient complained of right sided abdominal pains, which were regarded as probably biliary in origin It was found that she suffered from nephrolithiasis Roentgenological examination showed no signs of myeloma On later occasions a palpable lump in the abdomen was noted, but nothing pathological was demonstrated roentgenologically She was readmitted in June 1960 complaining of abdominal pain, weight loss and tiredness At this time, roentgenological examination showed a carcinoma of the cardia and the patient had dysphagia At the Surgical Clinic it was found that the carcinoma was inoperable and the patient was transferred to the Hospital for Chronic Diseases She died on Aug 31, 1960 On autopsy, a large carcinoma in the gastric fundus with wide spread lymphoglandular and intraabdominal metastases was found The bone marrow was examined microscopically and did not show any signs indicating myeloma *Plasma cells were found in the outer zone of the primary tumour and in the connective tissue of the infiltrated lymph glands*

It seems possible that there might be some connection (antibody formation??) between the carcinoma, the plasma cells and the monoclonal type γ globulins in this patient Further discussion of other connections between carcinoma and M-type globulins may be found in reports by Waldenstrom (18) and Heremans et al (5) a o The following case history also points out these connections, and is of special interest because this patient had both myeloma and wide spread lymph gland metastases, probably from a prostatic carcinoma

331 M S Man born in 1880, had a previous history of prostatic troubles In May 1959 he suffered a right sided hemiplegia His acid phosphatase was *not increased* Roentgenological examination revealed no signs of myeloma in skull or spine At this time he had only a slight anemia with 3 9 mill R B C and an ESR of 68 mm The patient's γ fraction contained a narrow band (3 2 %), with a low hexose content, which penetrated starch gel The sternal puncture revealed an increased number of plasma cells The patient died in December 1959, and the post mortem showed definite signs of myelomatosis, adenocarcinoma lymphonodorum mediastini et paraaort No primary tumour was found, but a prostatic carcinoma was suspected The prostate was not examined microscopically

On the whole, the combination of myeloma and carcinoma is not commonly found in our material of 93 consecutive patients from Malmo We know of one male patient with a gastric carcinoma and M S with prostatic carcinoma, and two female patients with cancer pancreatis and cancer coli This is completely different from macroglobulinemia, where carcinoma is quite common The difference could be explained by the fact that macroglobulinemia is longer lasting and more benign than myeloma The carcinoma in the former disease may, therefore, be the real reason for admission to the hospital, where the macroglobulinemia is detected On the other hand, the very common combination could indicate a causal relationship

The following two cases might well represent early myeloma, but in spite of a rather long period of observation, no certain diagnosis has been established Both patients have had carcinoma and their globulin increase is caused by a γ_{1A} fraction

was normal and an ESR was about 30 mm Her electrophoretic pattern remained the same Her pathological protein was a typical γ with a low hexose content and a typical immunoelectrophoretic γss behaviour

We have seen several patients with monoclonal hyperglobulinemia who have suffered from severe depressions (see cases A S G P and M C) It was therefore thought that there might possibly be a connection between the two disturbances and we have tried to treat the patients G P M C and A S with Melphalan During Jan 1961 G P had a short course of Melphalan with some leukopenia The total dose was 90 mg + 70 mg As this was well tolerated treatment was continued and she had in all 268 mg Melphalan There was no very definite effect on her psychical condition In June it was found that she *had an infected cutaneous carcinoma* on the left leg This was treated radiologically with good results There was no marked effect on the γ globulins and a new course of Melphalan was started in Jan 1962 There was neither objective nor subjective improvement The patient developed some anemia her Hb dropped to 6 8 g% and her R.B C to 1 8 mill Melphalan therapy was stopped after she showed signs of thrombocytopenia and three units of blood were given After that her condition improved Her last blood count on Oct 1963 R B C 2 9 mill Hb 11 0 g 100 ml W B C 4 100 platelets 226 000

141 S I Woman born in 1889 As early as 1944 it was found that she had an ESR of 68 mm In 1947 a hypernephroma was suspected and the patient was examined at the Surgical Clinic Her ESR at that time was 50 60 mm without any definite signs of disease In 1950 she was admitted to the Medical Clinic with an ESR of 93 mm Her thymol test gave very high values with a normal total protein Roentgenological examination of the skull and sternal puncture (on Dec 12th 6 plasma cells) showed nothing very remarkable On the third right finger she had a curious swelling the size of a hazel nut The following ESR values were found in the next years 1953 85 mm 1954 98 mm, 1955, 97 mm and 1956 93 mm In 1959 her ESR had increased to 118 mm She had a slight anemia Hb 78 % R B C 3 6 mill W B C and platelets were normal There was no proteinuria Urinary sediment revealed numerous white cell Her finger looked as before and she complained of pains in her back her shoulders and her hands Examination on Aug 19 1960 showed anemia R B C 3 3 mill Hb 11 0 g% and ESR 113 mm A lymphocytosis of 54 % was also noted Her γ globulin was then 2 7 % Neither roentgenological examination nor sternal puncture was possible at that time On examination in Sept 1962 Hb 75 % R B C 3 7 mill W B C 3 600 and platelets 242 000 Serum electrophoresis showed a practically unchanged condition There was no proteinuria Agglutination of thyroglobulincoated red cells 1/250 was noted Otherwise, serology was negative The last examination of this patient was performed on April 19th 1963 Serum albumin 5 4 % M component exactly constant 2 8 % (*fig* 4)

151 J H Man born in 1883 He was admitted in June 1957 for fever probably of renal origin Serum electrophoresis revealed a *typical small γ band* The lowered serum albumin was probably accounted for by the fever His γ globulin has since increased remarkably but the patient feels very well and X rays of his skull pelvis and spine in June 1962 showed no signs of myeloma There is no Bence Jones proteinuria His ESR is 26 mm There has been no recent increase in globulin

94 M F Woman born in 1889 In May 1956 pains in the right upper quadrant of the abdomen Diagnosis cholecystopathia Usually high ESR Electrophoresis M type γ globulin Slight increase of plasma cells Roentgen skeletal system not definitely pathological Sept 1958 no signs of myeloma in the skeleton but plasma cells 14 % No anemia after treatment of the patient s pernicious anemia (Low B_{12} in the serum) Since that time no anemia on continuous B_{12} treatment.

very feeble at that time In June the patient was able to walk with a stick and had no pain

In Nov 1958 the patient had pain in the right eye with vomiting and diplopia, and was readmitted with a right sided external oculomotor palsy The left patellar reflex and the lower abdominal reflexes were absent on the same side Improvement was slow

In July 1959 the patient had another attack of diplopia, and a left sided paresis nervi VI In August it was noted that the patient had impaired vision in the right eye Ophthalmological examination revealed thrombosis of the lower retinal veins on the right side He was readmitted in Aug 1959 with no paresis of the limbs Both the achilles and the patellar reflexes were normal, and his ophthalmological condition continued to improve Roentgenological examination and sternal puncture (plasma cells 2 8 %) showed no signs of myeloma Serum electrophoresis as before His ESR was 13 mm

I saw the patient many times after that His condition was improving continually His ESR was 10 mm Extensive serology was negative In April 1961 he suddenly developed abdominal symptoms and jaundice, with a greatly enlarged liver Death occurred May 4, 1961 The post mortem revealed a large carcinoma hepatis (see fig 3)

It is, of course, impossible to tell whether the monoclonal globulin was in any way connected with the carcinoma which obviously had a very rapid (final?) stage The possibility that the patient had a Bing Neel syndrome of unusually long duration must be considered

The following patient has not had any signs of carcinoma but his curious neurological picture (hypertension?) could possibly be related to the increase in γ globulin (Cf previous case H H)

332 A L Man born in 1905 In 1946 *hypertension* was noted In May 1959 the patient suffered a right-sided *hemiplegia and aphasia* His ESR was around 30 mm A narrow *γ fraction* was noted *Sternal puncture* revealed 3 2 % plasma cells There was very good restitution of his cerebral condition His ESR was only 10 mm, but a narrow γ band remained In Jan 1960 the patient suffered *paresis nervi VI of transitory nature*, with good restitution There was no anemia, his W B C was normal, there was no protein*uria and his ESR was 20 mm* The patient suffered from pain in the right leg but was otherwise feeling well X ray of the skull showed no foci He had a marked scoliosis but no skeletal destructions in the vertebrae Most remarkable is the fact that the electrophoretic *band had increased to 2 6 % and that the* serum albumin was pathologically low, whereas both *α fractions* were *increased* Sternal puncture could not be performed but the patient is still under observation and my impression is that he is developing a myeloma Last examination on Nov 19th 1963 *Good* general condition No anemia ESR 28 mm γ globulin M component 1 6 %

4 In the following cases, no signs of myeloma have developed in spite of quite high (but stable!) globulin values and a long follow up time (fig 3)

277 G P Woman born in 1902 This patient has a long and complicated history In Feb *1958* she was very nervous and the diagnosis of thyrotoxicosis was suspected There was also considerable weight loss with psychic depression She was admitted in Oct 1958 for further investigation Her ESR was at this time only *17 mm In spite of this serum electrophoresis showed* a γ globulin of 1 9 % *with a very sharp band in the slow γ* Sternal puncture revealed *4 8 %* plasma cells *in one* slide and *7 7 %* in another *The psychic condition of this patient deteriorated continuously* Another sternal puncture showed 6 0 % plasma cells and the patient was discharged undiagnosed She was *readmitted* in June *1960* with severe psychological disturbances being very tired with loss of initiative She was pale looked old and had developed an *anemia of 3 1 mill* (normochromic) W B C

as normal and an ESR was about 30 mm Her electrophoret c pattern rema ned the same Her patholog cal protein was a typ cal γ with a low hexose content and a typ cal mmunoelectrophoret c γ_{SS} behav our

We ha e seen several pat ents w h monoclonal hypergl obul nem a ho have suffered from se ere depress ons (see cases A S G P and M C) It as therefore thought that there m ght poss bly be a connect on between the t o distu ban es and we have tried to treat the pat ents C P M C and A S with Melphalan During Jan 1961 G P had a short course of Melphalan w th some leukopen a The total dose was 90 mg + 70 mg As this was well tolera ed treatment was con t nued and she had n all 268 mg Melphalan There was no ery defin e effect on her ps hical cond on In June it was found hat she *had an nfe ed cutaneous ca c noma* on the lef leg This was treated rad ol gically w h good results There was no marked effect on the γ globulins and a new course of *Melphalan* as started n Jan 1962 There was ne ther object e nor subject e mprove ment The pat ent developed some anem a he Hb dropped to 6 8 g% and her R B C o 1 8 m ll Melphalan therapy was stopped af er she showed s gns of *thrombocytopen a* and hree u ts of blood were g en After hat her cond on mproved Her last bl od count on O t 196 R B C 2 9 mill Hb 11 0 g 100 ml W B C 4 100 platelets 226 000

141 S L Woman born n 1889 As early *as 1944* was fo nd that she had an ESR of 68 mm In 1947 a hypernephroma was sus pec ed and the pat ent was exam ned at the Surg cal Cl n c Her ESR at that t me was 30–60 mm w hout any def n te s gns of disease In 1950 she as adm ed to *he Med cal Cl n c* h an ESR of 93 mm Her thymol es ga e ery h gh alues w th a normal total pro e n Roen genological examinat on of the skull and sternal puncture (on Dec 1 h 6 Plasma cells showed *no b ng very re* markable On he h rd right finger she had a curious swell ng the s ze of a hazel nut The follo ng ESR alues were found in the next years 1953 85 mm 1954 98 mm 1955 97 *mm* and 1956 93 mm In 1959 her ESR had increased to 118 mm She had a sl ght anem a Hb 78% R B C 3 6 mill W B C and platelets were normal There was no prote nuria Ur nary sed ment revealed nu merous wh te cells Her finger looked as before and she complained of pains in her back her shoulders and her hands Exam nat on on Aug 19 1960 showed anem a R B C 3 3 m ll Hb 11 0 g% and ESR 113 mm A lymphocytosis of 54% was also noted Her γ globul n as then 2 7% Neither roentgenolog cal examinat on nor sternal puncture as poss ble at that t me On exam nat on in Sept 1962 Hb 75% R B C 3 7 m ll W B C 3 600 and platelets 212 000 Serum electrophoresis showed a pract cally unchang ed cond t on There was no *proteinur a* Ag glut nat on of thyroglobulincoated red cell 1/250 was noted Otherw ise serology was negat e The last exam nat on of thi pat ent was performed on April 19th 1963 Serum albumin 54% M component exactly con stant 28% (fig 4)

151 J H Man born in 1883 He was ad *m tted* n June 1957 for fever probably of *renal origin* Serum electrophoresis revealed a *t p al small γ band* The lo ered serum al bum n as probably ac ounted for by the *fever* His γ globul n has s nce increased re markably but the pat ent feels very well and X rays of his skull pel s and sp ne n June 1962 showed no s gns of myeloma *There is* no Bence Jones proteinuria His ESR is 26 mm The e has been no recent ncrease n globul n

94 M F Woman born in 1889 In May 1950 pa ns in the righ t upper quadrant of the abdomen D agnosis cholecystopath a Usu *ally h gh* ESR E ectrophoresis M type γ *globu n* S ght increase of plasma cells Roen gen skeletal system not defin tely pathological Sept 1958 no s gns of myeloma in *the skeleton* but plasma cells 14% No ane *mia af er* treatment of the pat ent s pern cious *anemia (Low B_{12}* in the serum) S nce that *t me no* anem a on cont nuous B_{12} treatment

In April 1963 roentgen examination of cranium, thoracic and lumbar spine and pelvis no signs of myeloma Her γ globulin values have kept remarkably constant during the years We do not think now that this patient has any myeloma and are inclined to regard her as an instance of benign monoclonal hyperglobulinemia with a low back ground γ globulin (0 4 %) that may possibly be connected with her pernicious anemia (Schilling test positive, see Larsson (7) case 2)

93 K G Man born in 1881 In 1956 the patient had acute pneumonia His ESR came down to 38 mm *An M type serum γ globulin was found* Sternal puncture was not done The patient was re-examined by me in June 1959 His condition was excellent Blood normal Hb 91 % R B C 4 7 mill, W B C 4 600 differential count normal ESR 13 mm X rays of the skull were normal but he had vertebral osteoporosis with several collapsed vertebrae No sternal puncture was done In Aug 1962 blood values were normal with an ESR of 11 mm Roentgenological examination of the cranium was negative the pelvis and vertebral column showed signs that could indicate myeloma but were not conclusive The patient complained of no pain at all No anemia Electrophoresis showed albumin 4 2 % M component 1 1 % No sternal puncture

246 A P Man born in 1889 In Jan 1958 he had influenza His ESR was 80 mm After that time, the patient suffered several attacks of fever He had slight hypertension 210/110 Lymph glands spleen and liver were not palpable His Hb was 91 % and R B C 4 9 mill There was slight hyperbilirubinemia (3 0 mg/100 ml) with a negative direct reaction Hematological examination was normal Liver function tests were normal The patient was re examined on May 15 1961 His Hb was 90 % R B C 4 1 mill and his ESR 19 mm The bilirubin was still 2 9 mg/100 ml The patient was in excellent condition No skeletal survey was done Sternal puncture was not done Serum electrophoresis showed an increase in 7 S γss

114 K L Woman born in 1875 She has had hypertension for many years In Oct 1954 she was treated in the Hospital for Infectious Diseases Malmo, for signs of bronchopneumonia Later that year she developed auricular fibrillation *A narrow band in the γ region* was found but a skeletal survey was negative Her electrophoretic state has been determined several times the last in March 1961 (7 S γss) Roentgenological examination of the thoracic and lumbar spine and skull showed some decalcification but no signs of myeloma were evident at that time

118 O E Man born in 1888 In February 1957 he had angina His ESR was 47 mm Roentgenological examination demonstrated signs of bronchopneumonia Serum electrophoresis showed a *band in the slow γ region* (7 S γss) Sternal puncture revealed 6—8 % plasma cells This was repeated in March 1957, and also showed a slight increase in plasma cells There was no anemia W B C were normal The patient was re examined Aug 25 1959 He had no subjective symptoms His Hb was 86 % R B C 4 3 mill, W B C 3 800 and platelets 176 000 Skull X rays were normal

The patient was readmitted in May 1961 for a thorough examination He had some pain in the neck but roentgenological examination disclosed no signs of myeloma The cranium and cervical vertebrae were normal Sternal puncture in March 1962 revealed 3 7 % plasma cells

E M Man born in 1894 In June 1959 he had a duodenal ulcer *A narrow γ band* was accidentally discovered at that time Roentgenological examination of the skull showed suspicious foci in the cranium and *some local sclerosis* The patient was readmitted in Nov 1960 for acute melena He was transfused in the Surgical Clinic and then transferred to the Medical Clinic where no plasmocytosis and no change in the roentgenological picture were noted He still had the same type of electrophoretic pattern (γ band 0 4 %) as before The patient was readmitted in July

1962 for re examination He had severe neuritic pains following herpes zoster of the abdomen and seemed to be depressed Roentgenological examination of his pelvis and spine showed a compression fracture of the fifth lumbar vertebra and a dislocation of the lower endplate on the eleventh thoracic vertebra Both changes had appeared since 1959 His electrophoretic picture remained unchanged and the background γ was also low No abnormal urinary component was noted There was no anemia W B C and platelets were normal Sternal puncture showed 0 9 % plasma cells (in Nov 1962 1 5 %)

It is impossible to tell if this patient (E M) has developed a real myeloma In favour of this diagnosis are the fractures in the spine and the occurrence of herpes zoster, which is, of course common in myeloma

392 E N Woman born in 1897 Since *autumn 1959 she had* suffered pains in her back and right hip She was admitted to the Epidemic Hospital in March 1960 for high fever and signs of influenza *A narrow γ band* was found and the patient was transferred to the Medical Clinic where no other signs of myeloma were noted No definite plasmocytosis was evident on bone marrow puncture In Nov 1960 she did not suffer much from pain An extensive serological evaluation revealed an antistreptolysin titre of > 1,000 but was otherwise normal The patient was re-examined in March 1962 She had no anemia Her differential count and platelets were normal There was no proteinuria Skeletal survey showed no signs of myeloma Her albumin was 50 %, γ 2 1 %, background γ 0 1 %. Her antistreptolysin titre was found to be 1/80 000 serology being otherwise normal

312 A F Man born in 1884 His previous history is unimportant In March 1959 he developed thoracic pains which proved to be due to a myocardial infarction *Two narrow γ bands* (γ_{1A}) were subsequently noted There was no anemia and no signs of myeloma were evident on roentgenological examination The patient was re examined in Oct 1960 and had no cardiac symptoms and no anemia An extensive serological evaluation was negative In July 1961 there was no anemia and the electrophoretic pattern was as before

The following patient was thought to suffer from some systemic disease of slow development (reticulosarcoma?) The diagnosis of *essential* monoclonal hypergammaglobulinemia was found to be valid after negative autopsy findings

142 A K Man born in 1893 Between 1947 and 1957 periods of diarrhoea Roentgenological examination showed multiple large diverticula coli In July 1957 electrophoresis showed a *band in the γ fraction* The patient was readmitted in March 1959 with diarrhoea and loss of appetite Recently he had noted swelling of his legs and was admitted with marked edema and cyanosis Low blood pressure was noted X rays showed no signs of myeloma Steatorrhoea was found, a gluten free diet was *therefore instituted In* Jan 1960 there was still a moderate normochromic anemia The patient's ESR was around 30 mm There was a small narrow γ band ($7\ S_{ 19S}$) Treatment with cortisone had no influence on his intestinal condition Sternal puncture Jan 15, 1960 revealed 0 9 % plasma cells

The patient was readmitted in Jan 1961 and in April 1962 His steatorrhoea was still present but he was kept free from edema with diuretics His anemia progressed He had had paresthesiae in the legs since Jan 1961 and *was at this time decidedly ataxic* His serum B_{12} values were normal but his Schilling test showed pathological values There was no hematological response to the Schilling test or to continuous B_{12} medication The NPN rose terminally and the patient expired on May 6 1962 following an arterial occlusion in the right foot The autopsy showed chronic non specific inflammatory changes in the intestinal wall and systemic degeneration in the spinal marrow The patient also had contrac

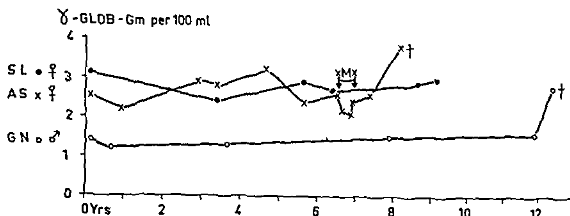


Fig 4 Three cases of essential benign monoclonal Obs' Different scale

ted kidneys but no amyloidosis or signs of myeloma were noted The etiology thus remains uncertain and no sign of any disease usually connected with monoclonal hyperglobulinemia was found

Two cases with essential benign monoclonal hyperglobulinemia, where myeloma may be definitely excluded (post mortem)

The following patient was first seen by Dr A Engel in Falun in 1946 The patient s plasma proteins have been of a peculiar kind and have been re examined repeatedly I am grateful to the late Dr L Thorling for some notes on the final disease The detailed case history will be published in a separate paper

19 G A Man born in 1890 The patient's history has been published previously (16) His clinical history is very uncharacteristic As early as 1946 a markedly increased ESR, 100 mm, was noted (for data on plasma proteins see below) There were signs of slight cardiac failure In 1951 the ESR was 70 mm and the patient was working normally Dr L Thorling examined the patient regularly and no serious clinical symptoms were found before Nov 1959, when the patient became acutely ill with diabetes and died on Nov 27th Macroscopically the post mortem showed nothing remarkable except some small bronchopneumonic foci Microscopically the heart showed nothing remarkable In both the liver and spleen, signs of considerable congestion were found, indicating an acute cardiac decompensation The kidneys showed post mortem autolysis No signs of amyloidosis or of diabetic nephropathy were discovered Paraprostatic thrombi were seen, otherwise, no changes in prostate or bladder were noted The lungs showed bronchopneumonic foci Bone marrow from the femur, vertebral bodies and the sternum was examined and had a normal composition with only solitary plasma cells The cranium contained only fatty marrow Nothing was found to indicate any systemic disease that could explain the plasma protein changes (I am grateful to Professor F Linell, Malmo, for the examination of the microscopic sections)

Serum proteins 1947 ESR 100 mm Howe salting out technique albumin 5 1, globulin 3 2 % Ultracentrifu ation 77 % 4 5 S, 23 % 7 S (Professor K O Pedersen Uppsala)

Electrophoresis (free electrophoresis in 1947, paper electrophoresis later)

	Tot prot	Alb	α_1	α_2	β_1	β_2	γ
1947	8 4	3 53	0 59		2 94		1 34
1955	7 3	4 4	0 3	0 5	0 6		0 75 + 0 8 (=pathol γ)
1959	8 8	2 8	0 6	1 3	0 7	0 6	1 6 + 1 2 (=pathol γ)

The last electrophores s was taken when the pat ent was acutely ill and this certainly expla ns the low serum albumin and the high α_2

It seems certa n that th s pat ent real ly had a ben gn essential d turbance of γ globul n synthesis for at least 12 years

The other example of essential hyper globul nem a with a narro v band which was publ hed by tl e author in 1952 (16) (case G B) has d ed s nce The post mor em d sclosed no illness that could account for the serum protein changes

The follow ng three pat ents H E E B and K A suffer from chron c rheumato d arthritis that might possibly be causally connected w th the hyper gammaglobulinemia It is also possible that the pat ents have two unrelated d seases The d sappearance of the in creased γ globul ns in ca e K A with ACTH therapy is remarkable

H E Man born n 1905 S nce May 1957 he has had a his ory of *h onic a th tis* w th an ESR of 25 mm S ernal puncture sho ed no h ng pathological (3 ? % plasma cells) *A na ow γ band* was noted In Jan 1959 he had pneumonia w th good reco ery on pen c ll n herapy He was some hat dyspne c The pa ent now has no swell ng of the leg no jo nt swell ng or pa ns n the back al hough he wears a corset for spondylolisthesis He s wo king full t me H s Hb is 97 % R B C 4 4 m ll ESR 12 mm There s no albun nur a The d fferent al count s nor mal The pa ent s last exam nat on was n Feb 1961 Extensi e serolog cal examinat on has been negat e tw ce

81 F B Man born in 1893 In 1953 the pa en had trans tory pa ns n the right shoulder In 1955 he had pain n the jo nts of the hands He was adm ed n June 1956 At th s t me compl te flex on of the f ngers of the left hand vas imposs ble and there was a 10 extens on defect on this de In the r ght hand there was a 30 extens on defect Both metacarpophalangeal jo nts were s ollen there were no toph Uric acid was 4 4 mg/100 ml Roentgenological exam nat on re vealed s gns of *rheumato d arth t s* in the hands Serum electrophores s showed a very *faint β γ band* (7 S γ_{SS}) The ESR was 8 mm Ster nal puncture showed 2 0 % plasma cells The pat ent has been followed ever s nce In Apr l 1958 he had some prote nuria and hyper tens on (210/105) The NPN was 45—38 mg/100 ml Re exam nat on n Sept 1959 showed the cont nued presence of a narrow band in β_2 0 8 % Otl erw se the serum pro te ns were normal The ESR in July 1960 was 7 mm There vas no anemia In March 1961 his Hb was 90 % R B C 4 7 mill and ESR 5 mm There as no prote nuria Serum electrophores s revealed a fa nt band as be fore There were no pecul ar serolog cal ab normal t es

440 F A Man born n 1903 S nce May 1960 he had compla ned of jo nt symptoms He was adm tted in Aug 1960 with s gns of *e e ch on c a th is* The ESR was 100—144 mm and an anem a hypos derem a and marked thrombocytos s of 6—800 000/mm³ were noted The pat ent also had a chronic leucocytos s He was readmitted n Oct 1960 for a hema olog cal re nvest at on He then had an anem a w h around 3 m ll R B C 7—8 g% Hb and a pers stent leucocytos s w th 80—90 % neutroph l cells There was no ncrease n basoph ls or eos noph ls His platelet count vas nea ly 1 m ll Serum iron was 20 γ/100 ml w th TIBC of only 200 γ/100 ml The jo nts were still act elv n olved The ESR was around 100 mm and a serum electrophores s showed a marked band n the rap d γ reg on and strong ncrease in α_2 with a low album n To al prote n 7 7 % albumin 2 7 % α_1 0 8 % α_2 1 2 % β 0 5 % β_2 0 5 % γ 1 2 + 0 6 % Total serology was negat e w th the except on of rheumato d factor 1 512 achryl plast 1 240 ant gamma 4 5 and CRP 4 mm

In sp te of treatment with Butazol d n Plaquenil and Deltison there was cont nued

deterioration The leucocytosis continued (max 21,000)

The patient was readmitted in Sept. 1961 The anemia had improved with a rise in Hb from 10 to 13 4 g% He had pain in practically all his joints, his appetite was very poor and there was considerable muscular wasting The patient was given ACTH in large doses (10 × 4) with dramatic effect He had also developed a very severe episcleritis which looked as though it could lead to perforation The eyes also responded well to ACTH, and the leucocytes fell to 10,000/mm³ The platelet count became normal and the pulse rate came down from 110 to 70 An eosinophilia of 1300—2200 cells disappeared and the eosinophil count fell to very low values

After lowering of the ACTH dosage there was a severe relapse but fluid retention had made it necessary to cut the dose His joint condition deteriorated considerably He had fever and a leucocytosis of above 20,000, and later developed abdominal symptoms and melena The leucocytes were 10,000 Intravenous ACTH resulted in dramatic improvement in the pains and the tachycardia He later developed signs of a hemolytic anemia The diagnosis of polyangeitis nodosa seemed indubitable On Jan 23, 1962, he lapsed into coma and died The autopsy showed residues of polyangeitis nodosa in the liver, mesentery and testes There were signs of acute glomerulonephritis and he had a septic condition There were no signs of myeloma, but the bone marrow in the vertebrae seemed to contain more plasma cells than normal Klebsiella and enterococci were grown from lungs, liver and spleen The autopsy obviously did not give any explanation of the monoclonal hyperglobulinemia, and myeloma may certainly be excluded It is impossible to tell if the band is in some way connected with the chronic arthritis or with the polyangeitis

Discussion and comments

In the group with observation times of more than three years (up to 5—9 years) the following possibilities may be discussed 1) this narrow monoclonal band represents an essential change in the γ globulin synthesis that remains forever clinically benign This change is obvious ly *always, with no exception, irreversible* Our studies give data regarding its stability during the years of observation It could also be possible that this represents 2) premyeloma, i e, that these patients, who have not had any clinical signs of myeloma for a number of years will later develop the full picture of this disease Here we have two possibilities either a) only a limited number of these patients will develop myeloma after some special further change has occurred in their plasma cells (one single plasma cell?), or b) they are all premyelomas and will sooner or later gradually develop myeloma This is, of course, an interesting problem from the point of view of tumour biology on the whole, and we shall try to analyse the material as it has developed until now

As a preparation for this, we have first studied our cases of multiple myeloma with a clearcut clinical picture in order to learn more about the beginning of this disease It is then quite remarkable to find that there are very few indirect indications of a long-drawn premyelomatous stage in our case histories The number of patients on whom an erythrocyte sedimentation rate (ESR) was determined some time before the diagnosis of myeloma was made is not large, but none of these observations seems to indicate that an unexplained, very high ESR had lasted for a long time This is quite contrary to the case of our patients with macroglobulinemia, where an unexplained, high ESR was often present several,

even many, years before any clinical symptoms appeared or the diagnosis was made more or less by chance It must be noted, however, that a number of our essential benign cases have not had re markably high ESR s

Our patients with myeloma have not been followed very long with regard to the rate of progression of their γ globulin values This is partly explained by the fact that patients with myeloma do not have a very long survival time, but is also a result of our recent interest in this point of view Several patients, how ever have been followed with electrophoresis for more than one year Two of these had absolutely clearcut myelomata already when admitted One male pa tient M A (fig 1), was already severely anemic when the diagnosis of myeloma was made His γ globulin at that time was 3 5 % and it rose rapidly in one year s time to 6 %, he died with a pro gressive anemia, with R B C falling as low as 1 5 mill The other patient J K (fig 1) had a very marked hypergamma globulinemia of over 6 % when he was admitted He had no definite anemia at this time In two years time his γ globu lin rose to 11 % he became severely anemic (2 5 mill R B C) and died The development in both these patients in dicates that there *may be a very rapid* in crease in γ globulins and a progressive anemia in myeloma Practically all our other patients where many protein de terminations have been made, have been treated with some cytostatic agent that might have had an influence on the pro tein metabolism Some data illustrating the rapid increase in globulins seen in all our other untreated patients with mye loma and repeated electrophoreses are also seen in fig 1

Some observations seem to indicate that a slow progression of the protein pic ture is not incompatible with the diagno sis of myeloma Patient E H, a woman, seems to be of considerable interest in this respect, as she has shown a slowly pro gressive increase in γ_{SS} globulin and plas ma cells and a progressive anemia but only after more than two years of follow up, was compression of one vertebral body found She is, therefore, unique We have *not yet observed a constant γ globulin value for several years that then changed over to a rapid increase* with signs of myeloma

There is one patient, however in whom this development could seem pos sible In patient A N, a woman 51 years old, *the γ_{SS} globulin values remained constant for one year* During the next year they increased considerably Her plasma cell count during the same time also increas ed from 11 to 18 % but she still had no signs of bone de truction A third case H M, showed steady increase in γ glo bulins until the diagnosis could be made from skeletal destruction All three pa tients were treated with Melphalan The effect was excellent both clinically and biochemically in E H and H M

This brings up the question as to whether slight changes in the plasma cell value are of any real diagnostic impor tance It has usually been said that a high plasma cell count is not in itself a proof of the development of myeloma, as it may have other causes If we group our benign cases in this paper according to the plasma cell counts in the bone marrow, it is obvious that only very few patients have a high count Several pa

tients were found with a plasma cell count above 5 %. Quite a number of patients have had plasma cell counts of 3—5 %, but this is, on the other hand, a very slight increase that can hardly be regarded as convincingly pathological.

One difficult question regarding this group is how to tell when the diagnosis of multiple myeloma should be made, i.e., the decisive prerequisites for the diagnosis. We know that the presence of the narrow *M-type γ globulin* is very characteristic even if there may be found other protein disturbances (hypogammaglobulinemia). *Sternal puncture* may often give valuable information regarding the plasma cells in the bone marrow. We have, however, seen rare patients with evident myeloma on roentgenological examination, where the plasma cell count on aspiration of the marrow was normal (15), obviously because the myeloma cells occurred in groups and the marrow between these was normal. The plasma cell count may vary considerably even between two simultaneous punctures. It is, therefore, impossible to exclude the possibility of myeloma on the basis of one normal sternal puncture. The same is especially true of the *roentgenological picture* that is usually markedly pathological, but may remain normal or only show slight osteoporosis until the end, even if such instances are rare (15). Typical focal bone destruction *and* M-type globulins constitute, with very few possible exceptions, an indication of myeloma (see, however, case O. L.).

Bence-Jones proteinuria is a rare symptom initially. It would appear that almost all cases of myeloma have *anemia* in the later stages, and one of the signs that we have been following systematically is the development of the red cell picture. It is also common to find that the serum albumin is low in myeloma. On the other hand, there is a definite inverse relationship between the serum globulin and serum albumin, and we find that most of our patients in the group of essential benign type discussed here, who have only moderate increases in γ globulin have a normal serum albumin if they are not in a febrile condition. We would, therefore, only like to state that the patients treated here have not, during a long period of observation, developed several of the signs that we regard as characteristic of multiple myeloma.

In summary, four questions seem to be of special interest in the differential diagnosis between malignant progressive myeloma and benign essential — but persistent — monoclonal hyperglobulinemia.

1. Does a high value for γ globulin per se mean that a malignant process is at work? (Figs. 1 and 2.) The answer seems to be yes. The only values above 3 % that were observed occurred in patients who later developed myeloma except in case S. L. and M. A. who had γ globulin values just above 3 %. On the other hand it must be remembered that we have a number of myeloma patients with quite low values.

2. Does a rapid increase in plasma globulin indicate that a myeloma is developing? The answer is probably yes. There are a few exceptions, however, for instance case M. A. (fig. 3), who died after two years observation time and did not have any clinical signs of myeloma then. She had an initial value slightly above 3 %.

3 Is the presence of anemia always a sign of malignancy? It seems as if erythrocyte values below 3 mill would indicate malignant process Anemia down to this level is quite common in our benign group, however

4 Is a low serum albumin in an afebrile patient a serious sign? A persistently low serum albumin is probably a serious sign Is must be remembered, however, that many of these patients have just passed through a febrile episode and therefore suffer from transitory hypalbuminemina

Summary

A number of patients with gamma globulin M components in the serum i e with monoclonal hyperglobulinemia have been followed for long periods of time In this material the M component never disappeared spontaneously Its level remained remarkably constant through the years, which is one of the main characteristics of this condition Moderate anemia is not uncommon Severe anemia and rapid rise in gamma globulin as well as M components above 3 g/100 ml probably indicate the development of myeloma The importance of a correct differential diagnosis between these patients, who need no treatment and patients with myeloma is pointed out

The theoretical implications of this disturbance in gamma globulin synthesis have been discussed elsewhere So far no indications of a transition between benign essential hyperglobulinemia and multiple myeloma were discovered although one patient (A N) could possibly belong to such a group

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Untersuchungen über den Kohlenhydratstoffwechsel

von

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Ich erlaube mir, die verschiedenen Ergebnisse über den Kohlenhydratstoffwechsel hauptsächlich in Tabellenform mitzuteilen unter Angabe der mir wichtig scheinenden Schlussfolgerungen. Tabelle I zeigt übersichtlich den Bedarf und Verbrauch von Sauerstoff, Kohlensäure, Eiweiss, Fett und Kohlenhydrat beim Menschen. Was der Mensch am meisten braucht, ist Wasser und Sauerstoff. Was den O_2 betrifft, so entscheiden, wie wir wissen, einige Atemzüge über Leben und Tod.

Tabelle II zeigt schematisch die CO_2-Ausscheidung nach Einnahme von Glukose bzw. Glukose + Casein, und nach Glukose bei Muskelarbeit. Es ist mir in diesem Zusammenhang angelegen, einige alte, aber sehr wichtige schwedische Untersuchungen zu demonstrieren.

Nach Zufuhr von 50 g Glukose beim nüchternen Menschen beträgt in Versuchen von J. E. Johansson die Steigerung der CO_2-Ausscheidung 7,8 g. Die Steigerung der CO_2-Abgabe ist bis zur Grenze von 150 g proportional der eingenommenen Glukosmenge. Die CO_2-Abgabe erfährt bei 200 g Glukosezufuhr keine Steigerung mehr, obwohl die Hyperglykämie noch weiter zunimmt. Die Stickstoffausscheidung im Harn bleibt nach Dextrosezufuhr auf dem Nüchternwert, ist also von der Dextrosezufuhr unabhängig geblieben.

In Selbstversuchen ergab die Zufuhr von 50 g Glukose allein 6,1 g CO_2, diejenige von 50 g Casein allein 4,2 g CO_2. Werden zu gleicher Zeit 50 g Glukose und 50 g Casein eingenommen, so beträgt die CO_2-Ausscheidung 10,2 g, welche Zahl auffallend genau der Addition der beiden Werte nach isolierter Einnahme der Stoffe entspricht. Ein Einfluss der KH-Zufuhr auf die Verarbeitung der Eiweisstoffe ist nicht vorhanden. Dasselbe Verhältnis ergibt sich bei der Glukosezufuhr während gleichzeitiger Muskelarbeit, wie schon Koraen nachgewiesen hat. Es trifft also nicht zu, wie oft behauptet wird, dass die während Muskelarbeit eingenommene Nahrung für die Muskeltätigkeit teilweise direkt verwertet wird. Die Nahrungsstoffe wer-

[1] Basel, Schweiz.

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TABELLE I Bedarf und Verbrauch pro Tag (g)

	O_2	CO_2	Eiweiss	Fett	KH
Bei Ruhe und Nüchtern (Selbstversuch)	505	560	88 6	89 8	107 5
Bei Arbeit und freigewählter Kost (Basler Arbeiter)	700—900	750—1,000	90—130	60—110	400—550

den erst dann für Muskelarbeit verbraucht, wenn sie zu körpereigenen Stoffen geworden sind

Nach 2—3 tägigem Fasten, d h nach Glykogenverlust, verursacht die Zufuhr von 50 g Glukose keine oder nur eine minimale Steigerung (+ 1 bis 2 g) der CO_2-Ausscheidung

Das Organ, das ohne reichliche Glukosezufuhr nicht auskommen kann, ist das Gehirn Ich darf noch erwähnen, dass Musfeld und ich beim Kaninchen eine Minute nach einer Insulininjektion schon Veränderungen am Elektroencephalogramm finden konnten, während die Blutzuckerveränderungen erst einige Minuten später beginnen

Was das Verhältnis Blutzucker, CO_2-Ausscheidung und Glykogenbildung betrifft, will ich Folgendes hervorheben Beim nüchternen Menschen (Selbstversuch) zeigt der Blutzucker 1 1/2 Stunden nach Zufuhr von 50 g Glukose wieder den Nüchternwert Die CO_2-Ausscheidung hat aber um diese Zeit ihr Maximum noch nicht erreicht Wenn man die Tierversuche berücksichtigt, so beginnt die Glykogenbildung erst 4 1/2 bis 6 Stunden nach der Fütterung, d h zu einer Zeit, da die CO_2 Ausscheidung sicher ihren Nüchternwert wieder erreicht hat

Werden Blutzucker und CO Ausscheidung nach einer längeren Fasten*periode bestimmt, so ergibt hier die Zu*fuhr von Glukose eine grössere Steigerung der Blutzuckerwerte als im Nüchternzustande, wobei die CO_2-Ausscheidung beinahe auf dem Nüchternwert bleibt Bang hatte schon gefunden, dass die Hyperglykämie bei Karenz-Tieren grösser ist als bei normal gefütterten

In der Literatur werden als KH Reserven das Glykogen und der Blutzucker angegeben Der Blutzucker sei die einzige Transportform der KH und ein Masstab der Assimilation Die eben erwähnten Resultate deuten schon darauf hin, dass diese Annahme kaum richtig sein kann Bang hat schon vor Jahren ausgedehnte Versuche mit Zuckerdarreichung per os, subcutan und intravenös durchgeführt Ich beschränke mich darauf, folgenden Versuch Bang's anzugeben Bei kontinuierlicher intravenöser Injektion einer 10 % igen wässerigen Glukoselösung findet nur in den ersten Minuten ein bedeutende Vermehrung des Blutzuckers statt, bei fortgesetzter Injektion, welche die grösste Menge des Zuckers umfasst, bleibt der Blutzuckerwert so gut wie unverändert „Der eingeführte Zucker verschwindet sofort aus dem Blute, dabei werden nur wenige

Prozente des zugefuhrten Zuckers im Harn ausgeschieden Bang untersuchte bei seinen Tieren die Leber (keine deutliche Glykogenspeicherung), die Lungen den Darm die Muskeln die Nieren das Knochensystem und kommt zum Schlusse — — — dass die Kohlehydratdepots welche den grossten Teil des Zuckers aufnehmnen noch unbekannt sind und — von der resorbierten Zuckermenge der allergrosste Teil weder in der Leber noch im Blut (noch in der Lymphe) nachweisbar ist — so ist er einfach verschwunden oder richtiger nicht aufzufinden

Erwahnenswert ist vielleicht auch die Tatsache dass beim Kaninchen und Menschen nach einer reichlichen Dextrosedarreichung der Blutzucker schon auf den Nuchternwert gesunken sein kann, auch dann wenn im Magen noch Dextrose vorhanden ist

Die vorhin mitgeteilten Tatsachen zwingen zu dem Gedanken dass der Blutzucker doch nicht die ausschliessliche Transportform der KH darstellt Diese Überlegung hat mich vor Jahren bewogen im Blute nach eventuellen vorubergehenden Zuckerdepots zu suchen Mit meinen Mitarbeitern Brauch Boulenaz und Noverraz haben wir den Gesamt Kohlenstoff und Gesamt Stickstoff des Blutes und deren Schwankungen untersucht Literaturangaben uber solche Untersuchungen sind mir nicht bekannt Nach Glukosezufuhr steigt der Gesamt Kohlenstoff des Blutes gewaltig an und zeigt stundenlang erhohte Werte (Tabelle IV Diese Steigerung des Kohlenstoffes ist im Serum nicht nachweisbar In einem anderen Versuch fand man nach 20 g Glukose eine Steigerung des

TABELLE II Gaswechsel CO_2 Ausscheidung (Nuchternversuch)

50 g Dextrose	+ 7 8 g CO_2 (Johansson)
100 g Dextrose	+ 14 0 g CO_2 (Johansson)
150 g Dextrose	+ 21 0 g CO_2 (Johansson)
200 g Dextrose	+ 21 0 g CO_2 (Johansson)
50 g Dextrose (D)	+ 6 1 g CO_2 (Gigon)
50 g Casein (C)	+ 4 2 g CO_2 (Gigon)
D + C	10 2 g CO_2
50 g Dextrose (D)	+ 7 5 g CO_2 (Korean)
Muskelarbeit (M)	+ 10 2 g CO_2 (Korean)
D + M	17 5 g CO

50 g Dextrose ergibt nach 3 tag gem Fasten keine Steigerung der CO_2 Ausscheidung (Johansson)

TABELLE III Versuch Praformierter Blutzucker 0 12 %

Injektionszeit (Min)	7	12	18	23
Injizierte Zuckermenge (g)	2	3	4	
Blutzuckerwert (%)	0 28	0 27	0 24	0 20

TABELLE IV Kaninchen 2 400 g

	Im Gesamtblut (%)		Im Serum (%)	
	C	N	C	N
9 00 Nuchtern	10 20	2 90	4 10	0 94
9 15 20 g Glukose	40 cm³ H O/os			
9 45	11 48	2 93	4 09	0 98
10 45	10 97	—	4 14	1 02
11 45	10 65	2 83	4 12	0 88

Gesamt C von 1 32 % des Blutzuckers von 0 089 auf 0 173 % d h ein Plus vom 0 084 % was nur 0 033 % Kohlenstoff entspricht

Tabelle V Mann, 34 Jahre, gesund

	Im Gesamtblut (%)			
	C	N	H_2O	Glukose
8 30 Nüchtern	9 98	2 81	81 56	0 112
8 45 100 g Dextrose in 100 cm³ H_2O				
10 45	10 40	2 67	81 18	0 100
12 05	10 56	2 61	79 04	0 98

Tabelle VIII Laevuloseversuch Kaninchen, Nüchtern

	C %	N %
9 00 Laevulose	9 44	3 00
9 25 20 g Laevulose in 40 cm³ H_2O/os		
10 10	11 69	3 24
11 10	10 38	3 27
14 00	10 59	3 13
17 00	9 80	2 86

Tabelle VI Glukose subcutan Mann, gesund

	Im Gesamtblut (%)			
	C	N	$\frac{C}{N}$	Zucker
9 00	9 37	2 45	3 82	0 105
9 50 Subcutan 10 cm³, 40%ige Glukoselösung				
10 20	9 43	2 48	3 80	0 190
10 50	9 54	2 62	3 64	0 150
11 45	10 01	2 90	3 45	0 125

Tabelle VII Intravenose Glukoseinjektion Frau, gesund

	Im Gesamtblut (%)		
	C	N	$\frac{C}{N}$
9 10 Nüchtern	9 17	2 59	3 34
9 25 2 g Glukose in 10 cm³ Wasser intravenös			
10 15	9 34	2 48	3 76
2 g Glukose = 0 8 gC +0 17×%, 5 l Blut ~ 0 77 g C			

Wie das nüchterne Tier verhält sich auch der nüchterne Mensch (Tabelle V) Der gesunde Mensch reagiert, wie dieser Versuch ergibt, auf Glukosedarreichung ebenfalls mit einer Steigerung das Gesamt-C des Blutes die stundenlang anhält Wird Glukose subcutan oder intravenös gegeben, so erhält man ebenfalls eine Steigerung des Gesamt-Kohlenstoffes Zum Unterschied mit der Darreichung per os oder intravenös, ergibt die subcutane Injektion eine deutliche Steigerung des Gesamt-Blutstickstoffes, während sich bei den anderen Applikationsweisen ein Sinken des Gesamt-Stickstoffes einstellt (Tabelle VI und VII)

Tabelle VIII zeigt den Gesamt-Kohlenstoff nach Laevulosezufuhr Nach Laevulosezufuhr ist die CO-Ausscheidung 2 mal grösser als nach Glukose, aber auch der C-Gehalt im Blut zeigt 2 mal höhere Werte als nach Glukose Die Bedeutung dieser Resultate wird später besprochen

Ein unerwartetes Resultat ergibt Tabelle IX Das Tier war stark abgemagert und wurde getötet In der Leber war keine Spur Glykogen zu finden (Prof Rössle)

Werden einem Kaninchen täglich grosse Dosen Glukose oder Laevulose neben anderer Kost verabreicht, so magert das Tier langsam ab und stirbt

TABELLE IX. Dauerversuch mit täglich 20—30 g Dextrose

	Im Gesamtblut (%)				
	C	N	H_2O	Zucker	Blut pH
Nach vorgehender Grünfutterernährung 8. Februar Nüchtern	8.79	2.30			
Seit 14. Februar Trockenfutter + täglich 20—30 g Dextrose 7. März	8.28	2.39			
Die Dextrosefütterung wird fortgesetzt 30. April	6.53	1.85	88.3	0.181	7.25

nach 1 1/2—3 Monaten. *Bei der Untersuchung findet man am Ende des Versuches merkwürdigerweise keine Spur Glykogen in der Leber.* Dabei wird Laevulose viel weniger gut vertragen als Glukose. Eine Ziege verhält sich ungefähr wie die Kaninchen. Nach 6 Monaten Dextrosefütterung plus gewöhnlicher Kost war die Leber glykogenfrei (einige Versuche mit Prof. Rössle). Einem Hund gab ich 4 Monate lang täglich 50—100 g Dextrose neben normaler Kost; das Tier blieb am Leben und zeigte keine Krankheitserscheinungen.

Im Gegensatz zur Glukosewirkung führt eine Insulininjektion zu einem gewaltigen Sinken des Gesamtkohlenstoffes des peripheren Blutes, und zwar auch hier in viel höherem Masse als es dem Sinken des Blutzuckers entspricht.

Sehr auffallend ist das gewaltige Sinken des Gesamtkohlenstoffes in der Muskulatur nach Insulin, das grösser ist als das Absinken im Blute und im Gegensatz dazu die starke Steigerung in der Leber auf 0.75 % C, was einer Kohlenhydratvermehrung von 1.9 % entspricht. Der Wasserverlust beträgt hier rund 2 %, während im Muskel der H_2O Gehalt mit 2 % gestiegen ist. Obwohl keine Glykogenanalysen gemacht wurden, möchte ich die Behauptung aufstellen, dass eine Steigerung von rund 2 % Glykogen innerhalb 2 Stunden nicht möglich erscheint. Wir haben ja oben die Resultate verschiedener Autoren erwähnt, wonach die Glykogenbildung viel langsamer vor sich geht. Zur Kontrolle unserer Analysenresultate haben wir eine Methode angewandt, die uns vielversprechend erschien: die *Infrarotphotographie*. Unsere Resultate, die mit Abbildungen publiziert wurden, ergaben Folgendes: *Im peripheren Blut tritt nach Glukosefütterung eine starke Zunahme der Absorption der Infrarotstrahlen ein,* und zwar während einiger Stunden, was der Zunahme des Gesamtkohlenstoffes ziemlich genau entspricht. *Nach Insulininjektion wird das Blut 2—4 Stunden später für Infrarot durchlässiger,* entsprechend dem Absinken des Kohlenstoffes.

Da das Plasma für Infrarot stets gleich durchlässig ist, so dürfen wir entspre-

TABELLE V Mann, 34 Jahre, gesund

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	C	N	H_2O	Glukose
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8 45 100 g Dextrose in 100 cm³ H_2O				
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TABELLE VI Glukose subcutan Mann, gesund

	Im Gesamtblut (%)			
	C	N	$\frac{C}{N}$	Zucker
9 00	9 37	2 45	3 82	0 105
9 50 Subcutan 10 cm³, 40%ige Glukoselösung				
10 20	9 43	2 48	3 80	0 190
10 50	9 54	2 62	3 64	0 150
11 45	10 01	2 90	3 45	0 125

TABELLE VII Intravenose Glukoseinjektion Frau gesund

	Im Gesamtblut (%)		
	C	N	$\frac{C}{N}$
9 10 Nuchtern	9 17	2 59	3 34
9 25 2 g Glukose in 10 cm³ Wasser intravenos			
10 15	9 34	2 48	3 76

2 g Glukose = 0 8 gC + 0 17 × %, 5 l Blut = 0 77 g C

Wie das nuchterne Tier verhält sich auch der nuchterne Mensch (Tabelle V) Der gesunde Mensch reagiert, wie dieser Versuch ergibt, auf Glukosedarreichung

TABELLE VIII Laevuloseversuch Kaninchen, Nüchtern

	C %	N %
9 00 Laevulose	9 44	3 00
9 25 20 g Laevulose in 40 cm³ H_2O/os		
10 10	11 69	3 24
11 10	10 38	3 27
14 00	10 59	3 13
17 00	9 80	2 86

ebenfalls mit einer Steigerung das Gesamt C des Blutes, die stundenlang anhält Wird Glukose subcutan oder intravenös gegeben, so erhält man ebenfalls eine Steigerung des Gesamt Kohlenstoffes Zum Unterschied mit der Darreichung per os oder intravenös, ergibt die subcutane Injektion eine deutliche Steigerung des Gesamt Blutstickstoffes, während sich bei den anderen Applikationsweisen ein Sinken des Gesamt-Stickstoffes einstellt (Tabelle VI und VII)

Tabelle VIII zeigt den Gesamt-Kohlenstoff nach Laevulosezufuhr Nach Laevulosezufuhr ist die CO_2-Ausscheidung 2 mal grösser als nach Glukose, aber auch der C Gehalt im Blut zeigt 2 mal hohere Werte als nach Glukose Die Bedeutung dieser Resultate wird später besprochen

Ein unerwartetes Resultat ergibt Tabelle IX Das Tier war stark abgemagert und wurde getötet In der Leber war keine Spur Glykogen zu finden (Prof Rössle)

Werden einem Kaninchen täglich grosse Dosen Glukose oder Laevulose neben anderer Kost verabreicht, so magert das Tier langsam ab und stirbt

TABELLE XII Gesamtkohlenstoffgehalt in der Muskulatur und in der Leber nach Insulin

	Vor Insulin (%)		2½ Std nach Insulin (%)		
	Gesamt C	H_2O	Gesamt C	H_2O	Differenz im C
Ruckenmuskulatur	12 38	74 04	11 50	76 01	—0 88
Blut	10 20		9 75		—0 45
			2 Std nach Insulin (%)		
Leber	14 35	72 23	15 10	70 28	+0 75 (+1 9 % KH)

spater auch von Macleod gefunden und in der Literatur ihm zugeschrieben

Eine meines Erachtens interessante Tatsache sei hier besonders hervorgehoben Nach 2—3 tagigem Fasten ergibt die Glukosezufuhr eine starkere Hyperglykamie aber eine viel geringere CO_2 Steigerung als im nuchternen Zustand Lasst man ein Kaninchen fasten so steigt der Gesamtkohlenstoff am 3 bis 4 Fasttag z B von 9 0 % auf 10 2 %

Der Zuckerkranke der einen hohen *Gesamtkohlenstoff* im Blute aufweist reagiert wie eben erwahnt auf Glukose mit sehr geringer oder keiner Steigerung der CO_2 Abgabe Die weiteren Tatsachen dass beim nuchternen Menschen oder Tier die Glukosezufuhr mit einer starken Steigerung der CO_2 Ausscheidung und deutlichen Erhohung des Gesamtblut C verbunden ist wahrend beim 2—3 Tage hungernden Menschen oder Tier die Glukose keine deutliche Steigerung der CO_2 Abgabe bewirkt scheinen im Zusammenhang zu stehen mit der anderen Tatsache dass das hungernde Individuum und der Diabetiker einen hohen Nuchternwert des Gesamtblutkohlenstoffes aufweisen Die Schlussfolgerung erscheint mir beinahe zwingend, das *die Steigerung der CO Abgabe nach Zuckerzufuhr mit der Steigerung des Gesamtblutkohlenstoffes in Zusammenhang gebracht werden muss* Zu Gunsten dieser Anschauung spricht die Tatsache, dass nach Laevulosedarreichung die Steigerung der CO_2 Abgabe wie auch diejenige des Gesamtkohlenstoffes im Blute 2 mal grösser ist als nach Futterung mit der gleichen Menge Glukose, also ein auffallender Parallelismus der Steigerung dieser beiden Werte

Die starkere Hyperglykamie beim hungernden Individuum nach Glukosezufuhr lasst sich vielleicht dadurch erklaren dass das Gesamtblut mit den C-Substanzen schon mehr oder weniger gesattigt ist and nur noch wenige neue Quantitaten bilden und aufnehmen kann

Vor Jahren habe ich die Vermutung ausgesprochen dass *die Belichtung des Korpers für den Stoffwechsel eine Rolle spielt* Wird ein Kaninchen 1/2—3 Monaten dauernd in dunkelrotem Licht gehalten,

TABELLE X Insulin Versuche Die starke Wirkung des Insulins wie die der Glukosezufuhr ist im Serum nicht vorhanden

		Im Gesamtblut (%)		Im Serum (%)	
		C	N	C	N
Kaninchen Nr 92					
7 45	Nüchtern	8 77	2 62	4 30	1 06
8 00	10 E Insulin				
9 50	Krämpfe	7 93	2 13	4 33	1 05
10 00	10 cm³ 30% Glucose subcutan				
10 30		8 82	2 44	4 27	1 02
Hund nüchtern				Blutzucker	
9 30		10 60	2 71	0 093	
9 50	*20 E Insulin subcutan*				
12 00	Krämpfe	9 70	2 76	0 038	

TABELLE XI Kaninchen Nach subcutaner Injektion einer 50%igen Glukosezufuhr schnellt der Blut C innerhalb von 10 von 9 46 auf 10 74%

		Blut C (%)	Blutzucker (%)
9 15	Nüchtern	10 30	0 10
9 35	1 cm³ Insulin subcutan		
10 35		9 15	0 051
11 35		9 46	
11 50	(Krampf) 5 g Glukose in 50% Lösung s c		
12 00		10 74	0 075

chend den C-Analysen im Serum, den Schluss ziehen, dass nach Glukosedarreichung *die Glukose mehrere Stunden in einer nicht reduzierenden Form in den Blutkörperchen aufgestabelt wird* und erst spater zum Teil in der Leber als Glykogen erscheint oder in der oben erwähnten Form vom Organismus verwertet wird Dass im nüchternen Zustande nach KH Zufuhr bei normaler Insulintätigkeit, eine reichliche und sehr prompte Fettbildung stattfindet, ist schon aus vielen Ergebnissen der Literatur mit Sicherheit anzunehmen

Photographiert man die Organe von Kaninchen nach Glukosefutterung bzw *nach Insulin, so findet man hauptsächlich im Aussehen der Leber starke Differenzen* Die Leber ist 1 1/2—2 Stunden nach Glukosedarreichung fur Infrarot durchlässiger als die Leber des Kontrolltieres, während sie 2 Stunden nach einer Insulininjektion am wenigstens durchlässig ist Weniger deutlich ist die Differenz im Gehirn, aber auch hier erweist sich die Photographie des Gehirns nach Glukose etwas heller als das des Kontrolltieres, während das Gehirn des Insulintieres für Infrarot eher weniger durchlässig ist Die Muskulatur ist bei allen 3 Tieren für Infrarot gleich stark durchlässig

Von einer Glykogenbildung in der Leber nach 2—2 1/2 Stunden kann weder nach Zuckerzufuhr noch nach Insulininjektion die Rede sein

Bei Diabetikern ist der Gesamtkohlenstoff im nuchternen Zustand meistens höher als bei gesunden Individuen Ausserdem *ist die Steigerung des Gesamtblut C* nach Glukosedarreichung stets niedriger als bei Gesunden Nun hat schon Johansson 1908 nachgewiesen, dass bei Diabetes die Zufuhr von Glukose in manchen Fallen eine geringe oder gar keine *Steigerung der* CO_2-Abgabe bewirkt Dieses Ergebnis wurde

andere, wahrscheinlich lebenswichtigere Aufgabe besitzt als nur Transportform kleiner Glukosenmengen zu sein Die Tatsache, dass die Dextrose die einzige Substanz darstellt, die praktisch quantitativ „bergauf“ (wie Wilbrandt sich ausdruckt) in den Tubuli ruckresorbiert wird, muss eine biologische Bedeutung haben

Harnstoffutterung sowie Darreichung von Ammoniumsalzen verursachen stets eine starke Steigerung des Blutammoniaks, die stundenlang anhalten kann Wichtig erscheint mir nun, *dass die Ammoniamie nach Futterung von Harnstoff oder Ammoniumsalzen durch Dextrosezufuhr rasch beseitigt werden kann* Im Versuch 225 sieht man trotz 20 g Harnstoffverabreichung nur eine minimale Steigerung des NH_3 N (Tabelle XVI) Diese Resultate deuten auf eine wichtige Aufgabe des Blutzuckers hin Diese Aufgabe aussert sich vielleicht auch in der Tatsache, dass bei zahlreichen Intoxikationen Narkosen, $MgSO_4$ regelmassig eine Hyperglykamie beobachtet wird Bedeutungsvoll ist es ferner dass diese „neutralisierende“ Wirkung auf Ammoniumsalze Harnstoff und gewisse Gifte nur auf die Glukose beschrankt ist Die Laevulose ist hier vollkommen wirkungslos Auch ist nach meiner Erfahrung bei Coma diabeticum und Insulinschock Laevulose nicht so wirksam wie Glukose

In diesem Zusammenhang sind folgende Zahlen bemerkenswert Im Blute findet man 0 02—0 03 mg % Ammoniak im Harn 0 7—1 1 g (Hammarsten) Der Harnstoffgehalt des Blutes betragt im Durchschnitt 24 mg % (20—40 mg % nach Leuthardt) derjenige des Urins 20—30 g Diese eigentumliche Wirkung der Glukose auf Blutammoniak nach Harnstoffutterung erscheint mir von Bedeutung insbesondere seitdem wir die blutzuckersenkende Wirkung des Sulfonylharnstoffes kennen und therapeutisch verwenden

Es ware interessant die Resultate am lebenden Individuum mit denjenigen zu vergleichen, die an sog uberlebenden Organen und in vitro gewonnen werden Es ist klar dass in vitro-Versuche, die man auf Lebende ubertragen will, mit den Ergebnissen am Lebenden nicht in Widerspruch stehen durfen, wenn sie als sichere biologische Tatsachen gelten sollen Solche Vergleiche sind leider nur selten gemacht worden, es wäre jedoch fur die biologische Wissenschaft eine sehr dankbare Aufgabe, sie in grosserem Masstabe zu unternehmen

TABELLE XVI

	Im Gesamtblut (%)		
	C	Zucker	NH_3 N
Beispiel Kaninchen			
8 45	9 80	0 09	0 02
9 00	20 g Harnstoff in 50 cm³ H_2O/os		
9 30	9 59	0 22	0 122
10 05	10 cm³ Glukoselosung 40% s c		
10 35	9 97	0 32	0 03
Versuch Nr 225 Kaninchen			
10 00	—	0 111	0 030
10 30	per os 20 g Harnstoff in 40 cm³ H_2O und subcutan 10 cm einer 40%igen Glukoselosung		
11 00	—	0 280	0 034
11 45	—	0 330	0 038
17 00	—	0 220	0 032

TABELLE XIII Diabetus mellitus Frau

	Im Gesamtblut (%)		
	C	N	Zucker
8 50 Nüchtern	11 66	3 21	0 366
9 15 50 g Dextrose in 150 cm³ H_2O			
9 45	11 82	3 28	0 505
10 25	11 13	3 35	0 555
11 15	11 04	3 16	—
12 00	11 14	3 18	0 463

TABELLE XIV Kaninchen 113

	Im Gesamtblut (%)		
	C	N	Zucker
3 Oktober			
9 10	11 18	2 61	0 102
10 15 30 g Glukose in 60 cm³ H_2O/os			
11 45	10 73	2 51	0 122
14 45	9 44	2 50	0 093
17 45	9 45	2 48	0 113
4 Oktober			
9 15	9 42	2 53	0 100

so ergibt die Glukosefütterung folgende merkwürdige Resultate Beispiel Kaninchen 113 Das Tier wurde am 12 August in ein dunkles, nur durch eine Scheibe von rotem Licht schwach erhelltes Zimmer gebracht Tabelle XIV gibt die Resultate einer Glukosefutterung und zeigt ein deutliches Sinken des Kohlenstoffes im Blute Das Tier wurde vom 31 Oktober an wieder bei Tageslicht gehalten Am 12 November wurde bei Tageslicht wieder eine Glukosefütterung vorgenommen (Tabelle XV), worauf man eine Erhöhung des Kohlenstoffes sah

TABELLE XV Kaninchen 113

	Im Gesamtblut C %
12 November	
9 00	10 01
9 50 30 g Glukose in 60 cm³ H_2O/os	
10 20	10 92
11 20	10 74
14 20	9 67

Tiere, die im Dunkelzimmer mit wenig rotem Licht längere Zeit gehalten werden, reagieren gegenüber Glukose wie auch gegenüber Laevulose nicht mehr wie Tageslichttiere mit einer Steigerung sondern mit einem Sinken des Gesamtkohlenstoffes des Blutes Auch die Hyperglykämie ist wesentlich geringer Man hat übrigens den Eindruck, dass diese Tiere die Glukosefütterung schlechter ertragen als Tageslichttiere

Nun erzeugt eine Insulininjektion bei im Dunkeln gehaltenen Tieren wohl eine Hypoglykämie, das Sinken des Gesamtkohlenstoffes fällt aber weg oder ist nur angedeutet Es scheint auch, dass diese Tiere die Insulininjektion besser ertragen als Tageslichttiere Krämpfe treten selten auf, und wenn sie auftreten, so später und schwächer als bei Tageslichttieren Selbstverständlich müssen die Tiere auch während der Versuche (Glukose und Insulin) im Dunkeln bleiben

Diese Ergebnisse zeigen, dass für das Tier wie für die Pflanze *das Licht für den Kohlenhydratstoffwechsel von Bedeutung* ist Es wäre reizvoll dieses Thema weiter zu bearbeiten

Zum Schluss sei auf die Möglichkeit hingewiesen, dass der Blutzucker eine

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First Medical Department University of Goteborg, Goteborg Sweden

Cerebral Hemorrhage in a Population after a Decade of Active Antihypertensive Treatment

By

M AURELL and B HOOD

Even before the breakthrough of active antihypertensive treatment the main causes of deaths in hypertensive disease tended slowly to shift (10) With improved treatment against congestive failure this formerly dominating cause of death was already losing terrain during the forties The advent of clinically practicable pressure lowering measures made this cause of death a rarity in large materials of actively treated hypertensives as was firmly stated in 1956 at the London symposium on hypotensive agents by Smirk and by ourselves (1 3 4 6 8)

We have earlier analysed the mortality in a large material (about 1000 cases) of actively treated severe hospitalised patients with hypertensive disease (5) In this material cerebrovascular lesions (87 cases out of 218) formed the most common cause of death Massive cerebral hemorrhage comprised roughly one third of all cerebrovascular lesions In this study it was pointed out that in contrast to the situation in myocardial infarction and uremia the group dying of cerebrovascular lesion largely consisted of therapeutic failures due to negligence or lack of understanding on part of patient or physician, or sometimes due to insurmountable obstacles against efficient treatment These obstacles included uremia, angina pectoris or general cerebral deterioration *existing before* and worsening during treatment Psychopathy and chronic alcoholism also made cooperation impossible Only *in a few* instances were side effects so severe as to make any degree of control impossible

Smirk and Hodge (7) have also reported a good reduction in the *frequency* of strokes (33 to 23 %) in treated hypertensive patients However they have taken into account only those *patients* who were under continuous *control* in their hypertensive clinic during the years 1959—1961 excluding those who stopped treatment for various reasons and those who ceased to cooperate with their clinic

We started active treatment in Goteborg in 1950 and have earlier reported

Submitted for publication February 24 1964

Summary

1 The simultaneous supply of glucose and protein shows no protein-saving influence of the carbohydrates The increase of the CO_2 elimination exactly equals the increase after the separate supply of the two foodstuffs

2 The supply of glucose per os, subcutaneously or intravenously causes a marked increase of total carbon in the blood of humans and animals, which is substantially higher and lasts longer than would be the increase of blood sugar

3 This increase of carbon is not found in the blood serum, therefore it must be localized to the red blood corpuscles After the introduction of glucose *per os* or intravenously the total nitrogen of the blood shows a very slight decrease, whereas subcutaneous injection causes an increase of the total nitrogen in the blood

4 After a supply of levulose the CO_2 excretion, and likewise the quantity of carbon in the blood, are twice as great as after the same supply of glucose (Johansson)

5 These results show that after a supply of glucose, the glucose is presumably stored in a non reduced form in the blood corpuscles for several hours, and only later is the non oxidized portion stored partly as glycogen and fat I should like to draw attention to the importance of these results for the understanding of the metabolism of the carbohydrates

6 If a rabbit is given 20—30 g of glucose of levulose daily beside its other food, the animal dies after six weeks to three months, there is no trace of glycogen in the liver

7 An insulin injection causes a rapid sinking of the total carbon in the blood, again in a much larger quantity than would be the case as regards the decrease of the blood sugar

8 Two and a half hours after an insulin injection in rabbits the total amount of carbon in the muscles decreases, for instance from 12 38 % to 11 50 % (the corresponding decrease in the blood was only — 0 45 %), whereas in the liver the carbon increased from 14 35 g% to 15 10 g%, corresponding to + 1 9 % carbohydrates This last increase can hardly be explained by a formation of glycogen

9 In diabetics the fasting blood carbon is usually much higher than in normal individuals After a supply of glucose there is only a small, if any, increase of CO_2 excretion (Johansson), the increase of carbon in the blood is also muss less than in normal individuals

10 Infrared photographs show a parallelism *with the analysis of carbon in blood and organs*

11 Animals kept for about one and a half months in a dark room with only a faint red light do not, like daylight animals, react to glucose or levulose feeding by an increase but by a decrease of total carbon The conclusion is, therefore, that for animals as well as for plants light is important for the metabolism of carbohydrates

12 The ammoniaemia after feeding with urea or ammonium salts is quickly eliminated by a supply of glucose These results point to an important function of the blood sugar

TABLE I Total material from the Sahlgren s Hospital

Year	Admitted	Dead	Autopsied	Percentage autopsies	Cerebral hemorrhage	Cerebral hemorrhage <65 years of age	Percentage of cerebral hemorrhage <65 years of age[1]	Cerebral hemorrhage in % of autopsies All	<65 years of age
1948	31 891	794	776	98	51				
1949	33 053	838	790	95	69				
Total	64 944	1 632	1 566	Mean 96 5	120	57	47 5	7 7	3 4
1960	43 806	1 385	1 35▯	98	70				
1961	46,239	1 511	1 451	97	79				
Total	90 045	2,896	2,806	Mean 97 5	149	47	31 7	5 6	1 7

[1] The decrease is significant $\chi^2 = 7\ 17$ $p < 0\ 01$

TABLE II Distribution of cerebral hemorrhages in age groups from Sahlgren s Hospital and referred to 10 000 inhabitants in Goteborg

Year groups	1948 + 1949 No	%	Inhabitants in Goteborg 1950	Dead per 10 000 inhabitants per 1 year	1960 + 1961 No	%	Inhabitants in Goteborg 1960	Dead per 10 000 inhabitants per 1 year
30 – 34	3	2 ▯	30 909	0 5	—	—	27 776	0
35 – 39	2	1 7	30 316	0 3	—	—	23 037	0
40 – 44	1	0 8	29 285	0 2	—	—	31 229	0
45 – 49	5	4 2	25 393	1 0	4	2 7	30 363	0 7
50 – 54	8	6 7	22 530	1 8	7	4 7	28 703	1 2
55 – 59	20	16 6	19 874	5 1	18	12 1	24 185	3 7
60 – 64	18	15 0	16 861	5 4	18	12 1	20 719	4 4
65 – 69	23	19 ▯	12 436	9 4	17	11 4	16 898	5 0
70 – 74	24	20 0	8 476	14 2	28	18 8	12 648	11 2
75 – 79	5	4 2	5 041	5 0	23	15 4	7 729	14 9
80	11	9 2	3 49▯	15 8	34	22 8	5 667	31 7
Total	120	100 0			149	100 0		

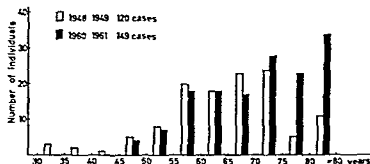


Fig 1 Age distribution of all individuals with lethal cerebral hemorrhage in 5-year brackets.

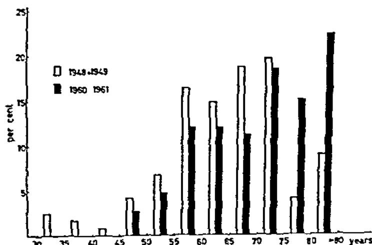


Fig 2 Percentage distribution of all individuals with lethal hemorrhage in 5-year brackets.

prolonged survivals in all the severe varieties of hypertensive disease. We have during recent years formed the impression that, in age groups below 55 years, cases admitted with a massive cerebral hemorrhage were becoming so rare that sometimes a whole group of students after several months could deny ever having seen this classical picture When such cases did arrive we have also the impression that they either had never sought medical advice or had been totally unaware of previous hypertension These impressions seem to suggest that active antihypertensive treatment had become widespread enough to begin to affect the patterns of death in the whole hypertensive population, not merely in the material under our own control

We decided to seek whether there were any solid grounds for these impressions by analysing the autopsy records in Göteborg from the years 1948 and 1949 as compared with the years 1960 and 1961 We also analysed case records for all those aged up to 65 with autopsy-proven cerebral hemorrhage, for information concerning any previous active antihypertensive treatment

Material and methods

Sahlgren s Hospital with about 2,500 beds is the only general hospital in Göteborg for emergencies The main part of our analysis thus consists of the autopsy records from this hospital (figs 1 and 2, tables I and II) However, change in treatment might conceivably have prolonged lives somewhat and enabled

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45 49	5	4 2	25 393	1 0	4	2 7	30 363	0 7
50 54	8	6 7	22 530	1 8	7	4 7	28 703	1 2
55 59	20	16 6	19 874	5 1	18	12 1	24 185	3 7
60 64	18	15 0	16 861	5 4	18	12 1	20 719	4 4
65 69	23	19 1	12 436	9 4	17	11 4	16 898	5 0
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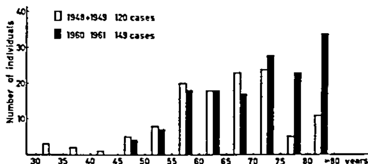


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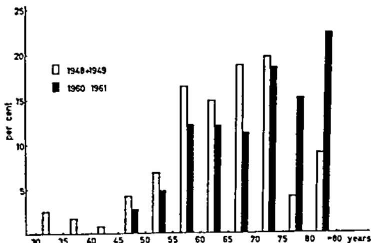


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TABLE IV Cerebral hemorrhage in the material from the chronic hospital (Vasa) and death certificate autopsies

Age groups	Chronic hospital 1949 Cerebral hemorrhage	Death after prolonged survival[1]	Total	1961 Cerebral hemorrhage	Death after prolonged survival	Total	Death-certificate autopsies 1948+1949 Cerebral hemorrhage	1960+1961
30–34						71		
38–39								
40–44								1
45–49	1		1					2
50–54		1	1	2		2	3	
55–59	2	4	6					4
60–64	2	3	5	1		1	4	
65–69		4	4	1	3	4	1	1
70–74	2	1	3	1	5	6	2	1
75–79		3	3	1	5	6	1	2
>80		1	1	4	5	9		2
Total	7	17	24	10	18	28	11	13

[1] Occurring in pulmonary embolism bronchopneumonia etc

doubled frequency in the older ones (table II)

The percentage of deaths in cerebral hemorrhage under 65 years of age has during the period fallen from 3 7 per cent to 1 7 per cent This corresponds to the decrease of lethality of cerebral hemorrhages in age groups under 65 during the period

In the analyses of the autopsies from the hospital for chronic diseases the same trend of decreased incidence of cerebral hemorrhage within lower age groups in the latter period is clearly to be observed

The death-certificate autopsies cover only small numbers The above trend is hardly clearcut and no valid conclusion can be drawn other than that cerebral hemorrhage in a large series of death-certificate autopsies form only a small and insignificant group among other causes of death (suicide traffic accidents, drowning etc)

We have asked ourselves if the patients dying of cerebral hemorrhage during the latter period (1960—1961) had active therapy and if so what was the general quality of the treatment? We have for this purpose analysed the clinical histories in the 50 patients of 65 years of age and thereunder dying in 1960 and 1961

Table V shows rather clearly that a number of these patients (15 of 29) received no active treatment at all up to the stroke In another group (11 of 29) the case reports leave doubt as to whether

TABLE III Total material from the chronic hospital (Vasa) and death-certificate autopsies

	Chronic hospital (Vasa)						Death certificate autopsies		
Year	Admitted	Dead	Autopsied	Percentage	Dead in cerebral hemorrhage and sequelae	%	No	Cerebral hemorrhage	%
1948							212		
1949	1,611	707	451	64	24	5 3	217		
Total							429	11	2 6
1960							369		
1961	1,602	658	617	94	28	4 6	380		
Total							749	13	1 7

the patients to be transferred to the hospital for chronic diseases (also one for Goteborg) Therefore, we have analysed the autopsy records in this hospital but only for the years 1949 and 1961 respectively for deaths either *in acute cerebral hemorrhage* or in complications during a prolonged aftermath of cerebral hemorrhage (tables III and IV)

Death is usually not immediate in cerebral hemorrhage and the great majority of cases will be admitted to the acute hospital However, a certain number of patients still die outside the hospital If the patient is unknown to a physician, or if his physician has any doubts about the cause of death, the coroner s office will have a death certificate autopsy performed These records have been analysed for the years 1948 and 1949 as well as 1960 and 1961 Results are given in table III and IV

Table I gives number of admissions number of deaths (2) and number of analysed autopsies as well as the number of autopsy proven cerebral hemorrhages in the respective years We have included cerebral, cerebellar and pontine hemorrhages Aneurysms, epidural and subdural hemorrhages have been excluded as have those occurring after severe traumatic injuries of the head and in toxemia of pregnancy

Fig 1 gives the number of cases according to age groups and fig 2 gives the percentage of hemorrhages within the age groups the late period 1960 and 1961 being compared with the early period 1948—1949

Results and discussion

The striking shift of the age occurrence of cerebral hemorrhages *in the material* from the Sahlgren's Hospital (figs 1 and 2, table II) is easily seen, as is the total reduction as expressed by the percentage among those autopsied of deaths due to cerebral hemorrhage (5 6 per cent in the late period is compared with 7 7 per cent in the early one)

The numbers of deaths in cerebral hemorrhage per 10 000 inhabitants in Goteborg (vital statistics available for the years 1950 and 1960 (9)) also show this age shift around 75 years of age, in that there is a substantial reduction in younger age groups contrasting with the

The general decrease of cerebral hemorrhage as well as a shift to higher age groups (above 65 years) is a hardly deniable fact within this population after the first decade of antihypertensive treatment It seems as if drug treatment of hypertensive disease has become so widely accepted as to change the general patterns of death in the whole hypertensive population Still better results will be possible with constant attention to establish a good blood pressure control even to the point of moderate side reactions

Conclusions and summary

In Goteborg where active antihypertensive treatment began in 1950 and has been pursued quite widely since 1952 we have analysed autopsy records from the major hospital for acute diseases and from the chronic disease hospital as well as death certificate autopsies both before the advent of active blood pressure treatment and after active treatment had been available for a decade

1 Cerebral hemorrhage as a cause of death in all autopsies has dropped from 7 5 to 5 6 per cent and there was a very marked shift upwards in age the percentage incidence of cerebral hemorrhage under the age of 75 being lower in the later period while higher in the earlier

2 Further there has been a significant decrease in cerebral hemorrhage mortality under 65 years of age (47 5 % to 31 7 %) although the population at risk has increased markedly and this cause of death has almost been eradicated under 45 years of age

3 In those dying in 1960 and 1961 below the age of 65 by cerebral hemorrhages and aware of previous hypertension no or inadequate therapy had been given No case was under continuous good regulation of the blood pressure at the time of the stroke

4 As seen above and in an earlier analysis of the mortality of cerebrovascular lesions in our clinical material there is very strong evidence that good blood pressure control can prevent cerebral hemorrhage in all younger age groups

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TABLE V Analysis of patients dying of cerebral hemorrhage 1960 + 1961, aged 65 and under

				Hypertensive disease known before final admission			
					Active treatment		
	Total no	Evidence of hypertensive disease at autopsy	Hypertensive disease not known before final admission	No	Definitely tried	Not known	Not tried
Column no	I	II	III	IV	V	VI	VII
Males	23	23	13	10	1	1	8
Females	27	25	6	19	2	10	7
Total	50	48	19	29	3	11	15

Column I 14 of 23 males and 22 of 27 females came from low socio-economic classes
Column II All but 2 cases showed evidence of hypertensive disease at autopsy Those 2, both females, have had advanced but healed pulmonary tuberculosis
Column III 40 % of the hypertensives
Column IV 60 % of the hypertensives
Column V The only male was an active businessman who did not follow the regimen The 2 females had chronic pyelonephritis with poor blood pressure control
Column VI 8 females controlled by practitioners medication at least eventually included only thiazide or reserpine
Column VII Active treatment not tried

they received active treatment Only a few (3) had received active treatment but the blood-pressure control was inadequate Not a single patient was under continuous, well-regulated and well-controlled antihypertensive treatment at the time of hemorrhage

This means that only about half of the known hypertensive patients have tried some kind of antihypertensive treatment, whether active or not About 40 per cent of the autopsied had no knowledge of their hypertension prior to the stroke

The absent or very sad state of therapy in those below the age of 65 suffering a cerebral hemorrhage during 1960—1961 seems very striking In our earlier analysed clinical material of about 1,000 mostly severe hypertensives, where active treatment had been induced during a hospital admission, we had 87 lethal cerebrovascular lesions The great majority occurred in patients who may be regarded as our worst therapeutic failures There was in half of them disruption of treatment and generally a low degree of control due to a variety of reasons which we have analysed (5) It was thus a definite rarity for cerebrovascular lesions, both hemorrhage and encephalomalacia, to occur with good or even moderately good control The implication of this is clear Patients below 65 years under good control do not die by cerebral hemorrhage and also seldom by encephalomalacia

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First Medical Service Sahlgren s Hospital University of Göteborg, Goteborg, Sweden

Circulatory Effects of Long-term Anticholinergic Treatment with Poldine and l-Hyoscyamine

By

Gustav Schröder and Gerhard Dotevall

Anticholinergic drugs have been used in the treatment of circulatory disorders as well as in diseases affecting the gastro-intestinal tract The influence of these drugs on the circulation in man has been studied only to a limited extent This is especially true of the long term effect during continuous oral therapy The introduction by Sun and Shay (14) of treatment with optimal effective doses of anticholinergic drugs for patients with peptic ulcer has emphasized the lack of information regarding the circulatory effects

The present report describes the result of hemodynamic studies in patients with peptic ulcer before and during continuous treatment with two different compounds with anticholinergic action (hyoscyamine and poldine respectively)

Material and methods

Thirteen men and one woman (S S) hospitalized because of peptic ulcer were studied (table I) Judged from history physical examination and ECG they were without cardiovascular disease No patient was bleeding when the study was made Two patients had (OK 31 and SS 52) low hematocrit values of 32 and 25 respectively all others having hematocrits between 38 and 48 All but one young obese man (B B) were of normal body build

Hemodynamic studies were made in the morning in a post absorptive state Smoking was forbidden After local anaesthesia a polyethylene catheter was placed in the brachial artery and another radiopaque catheter under fluoroscopic guidance in the right atrium from an antecubital vein using the Seldinger percutaneous technique (13) After at least half an hour of rest blood pressures were recorded by means of variable inductance transducers (Elema) and a multichannel photographic oscillograph Expired air was collected in a Douglas bag for five to seven minutes In the middle of this period, cardiac output was determined with the dye dilution technique using sulpho-bromophthalein (15) The serum dye concentrations were read from a Beckman B densitometer The expired air was analyzed using the Scholander apparatus After another rest period of at least half an hour the procedure was repeated with the patient sitting comfortably in an armchair

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After an equal rest period the subjects performed exercise sitting on an electrically braked bicycle ergometer for about ten minutes

Pressures were recorded before the work started and every second minute during work Expired air was collected between the seventh and tenth minute of work The cardiac output was determined on the ninth minute of work The zero level for transducers was placed 5 cm below the sternal notch when the patient was lying and in the third intercostal space in the sitting position

The work load was 600 kpm/min in all the hyoscyamine treated and in two of the poldine treated Four patients performed exercise twice with work loads of 300 and 600 kgm/min respectively The woman worked on 300 kgm/min only and one man on 600 and 900 kgm/min

The study was repeated after treatment following the same procedure The average duration of treatment was for hyoscyamine 5 7 days and for poldine 9 9 days

Six subjects were given hyoscyamine in slow release tablets (Duretter Hassle) and eight poldine as Nacton tablets(BRL) The doses were increased until light dryness of the mouth developed The mean dosage of hyoscyamine was 1 48 mg a day divided in three doses The corresponding dose for poldine was 29 6 mg a day The poldine tablets were given in equal doses four times daily The last dose was given half an hour before the study was started in the morning

In every hyoscyamine treated patient the non treatment study was made first In six of the poldine treated patients the non treatment study was made first and in two the study during poldine treatment preceded the non treatment study Poldine was withheld for at least one week before the hemodynamic study was repeated

The peripheral resistance was calculated according to the formula $\frac{BA_M - RA_M}{CO}$ and expressed in arbitrary units Left ventricular work and left ventricular stroke work were calculated as BA_M CO and BA_M SI and expressed in kpm/min and pm respectively (BA_M and RA_M = brachial arterial and right atrial mean pressures in mm Hg CO = = cardiac output in l/min SV = stroke volume in ml)

Mean values and standard errors were calculated according to the common formulae

P values of differences were obtained by t test and t was calculated according to the formula $t = \frac{M_{diff}}{\varepsilon_{diff}}$ (M_{diff} = mean value of differences and ε_{diff} = standard error of the mean value for differences)

Results

The mean values, the standard errors and the P values are given in table II for the poldine treated and in table III for the hyoscyamine treated patients

The *heart rate* was unchanged during rest in the recumbent position and during exercise after the two drugs During poldine treatment when the patients were sitting the heart rate increased when compared with the recumbent position ($p < 0.01$) and also when compared with the heart rate in the sitting position before poldine treatment ($p < 0.05$) No orthostatic change was seen during hyoscyamine treatment

During poldine treatment the *brachial arterial mean pressure* was higher as compared with before treatment in the sitting position ($p < 0.05$) and decreased ($p < 0.02$) when changing from the recumbent to the sitting position No change occurred during exercise on poldine treatment In the hyoscyamine treated patients the systolic pressure during exercise was lower than before treatment ($p < 0.05$) No other change of arterial pressure was obtained during hyoscyamine treatment

TABLE I

Case	Age (yrs)	Height (cm)	Weight (kg)	Dose $\frac{mg/day}{no\ of\ days}$ + last dose	Remarks
Poldine treated					
GR	19	184	60 3	$\frac{32}{>30} + \frac{50}{1} + 10$	–
BB	26	182	125 2	$\frac{16}{2} + \frac{32}{1} + \frac{40}{3} + 10$	Dryness in the mouth
LJ	29	184	68 2	$\frac{16}{1} + \frac{24}{1} + \frac{32}{1} + \frac{40}{2} + 10$	Dryness in the mouth Thirst
AK	35	186	86 0	$\frac{16}{5} + \frac{24}{5} + \frac{32}{3} + \frac{40}{1} + 10$	Dryness in the mouth
JN	36	176	74 7	$\frac{16}{2} + \frac{24}{2} + \frac{32}{2} + \frac{40}{1} + 10$	Dryness in the mouth
MK	40	179	70 2	$\frac{24}{2} + \frac{32}{5} + \frac{40}{1} + 10$	Obstipation Dryness in the mouth
SS	52	167	80 8	$\frac{32}{2} + 8$	Dryness in the mouth
GA	54	181	70 0	$\frac{16}{1} + \frac{24}{2} + \frac{32}{3} + 8$	–
Hyoscyamine treated					
RG	17	167	44 3	$\frac{0\ 8}{2} + \frac{1\ 6}{3} + \frac{2\ 4}{1} + \frac{3\ 2}{1} + 0\ 8$	Dryness in the mouth
SV	21	174	66 8	$\frac{0\ 8}{2} \quad \frac{1\ 2}{1} \quad \frac{1\ 6}{2} + 0\ 8$	Dryness in the mouth
KO	31	185	85 7	$\frac{1\ 2}{2} + \frac{1\ 8}{2} + \frac{2\ 4}{2} + 0\ 8$	Dryness in the mouth
SJ	44	175	71 3	$\frac{1\ 2}{4} + \frac{1\ 8}{1} + \frac{2\ 4}{1} + \frac{1\ 6}{1} + 0\ 8$	Dryness in the mouth Trouble with reading
KS	52	168	67 9	$\frac{0\ 6}{2} + \frac{1\ 2}{4} + 0\ 4$	–
TW	59	183	60 7	$\frac{1\ 2}{1} + \frac{1\ 6}{1} + \frac{2\ 0}{1} + 1\ 0$	Thirst

on a bicycle ergometer before (B) and during (D) long term poldine treatment in eight subjects

RA		LVW		LVSW		Oxygen cons (ml/min)		Ventilation (l/min)		RQ		Oxygen A V diff	
B	D	B	D	B	D	B	D	B	D	B	D	B	D
Recumbent													
2 4	2 7	9 80	11 06	143 5	151 9	295 5	272 9	10 44	10 02	0 814	0 829	40 9	34 6
0 6	0 5	0 96	0 48	12 8	7 3	21 6	18 6	0 76	0 64	0 029	0 046	1 7	1 1
			<0 10				<0 05						<0 01
<0 05	<0 001	<0 02	<0 005	<0 02	<0 001							<0 10	<0 005
Sitting													
2 0	−3 4	8 54	8 83	122 6	106 6	310 5	302 3	11 72	12 39	0 840	0 854	49 5	46 8
1 3	0 6	0 95	0 42	14 6	3 2	25 6	22 7	0 89	1 25	0 020	0 026	5 0	2 7
Exercise													
+0 6	0 4	22 4	21 3	156 8	140 9	1 693	1 527	51 73	49 55	0 889	0 959	124 6	112 0
1 9	1 3	2 8	1 3	20 9	7 7	124	85	2 69	3 24	0 031	0 023	12 1	5 4
							<0 02		<0 10		<0 10		

pressures (mm Hg) CO = cardiac output (l/min) SV = stroke volume (ml) $\frac{BA_M}{CO}$ = resistance
work kpm/min and pm beats respectively RQ = respiratory quotient Oxygen A V diff =

The *right atrial mean pressure* was unchanged after treatment with more pronounced orthostatic pressure decrease for both drugs

Left ventricular work and stroke work were unchanged after treatment with both drugs The orthostatic decrease was more pronounced during poldine treatment but disappeared during hyoscyamine treatment

The pulmonary ventilation and the respiratory quotient remained the same during treatment.

No ECG changes were seen during treatment and the subjective and objective working capacity remained unaltered

Discussion

This method for studying the effects of circulatory active drugs during continuous oral administration has been used repeatedly without complications (10 11 12) and with good reproduction of the results (8)

TABLE II Hemodynamic data during rest in the recumbent and sitting positions and during exercise Mean values, SE and P-values

HR		BA_S		BA_D		BA_M		CO		SV		$\frac{BA_M}{CO}$	
B	D	B	D	B	D	B	D	B	D	B	D	B	D
Recumbent													
68.4	73.1	135.5	137.8	79.5	83.8	97.9	103.6	7.28	7.84	106.9	108.3	13.8	13.4
3.1	3.5	4.6	4.0	2.6	1.7	3.3	2.3	0.52	0.43	7.3	6.5	0.8	1.1
					<0.10				<0.10				
	<0.01						<0.02	<0.005	<0.001	<0.05	<0.001	<0.005	<0.001
Sitting													
70.6	82.8	127.4	131.3	76.4	82.6	95.3	100.1	6.52	6.47	94.0	78.4	15.3	15.9
3.1	3.2	4.8	4.0	2.9	1.6	4.0	2.6	0.55	0.32	9.0	2.8	1.3	1.1
<0.05				<0.10			<0.05						
Exercise													
140.1	144.5	168.0	168.3	83.8	86.5	110.3	114.6	14.3	13.6	102.9	94.0	8.18	8.63
5.8	6.5	8.2	3.7	4.5	3.0	6.0	2.2	1.6	0.7	11.3	3.2	0.71	0.44

HR = heart rate (beats/min) $BA_{S\,D\,M}$ = brachial arterial systolic (S) diastolic (D), and mean (M) units RA = right atrial pressure (mm Hg), LVW and LVSW = left ventricular work and stroke arteriovenous oxygen difference ml/l

The *cardiac output* at rest was unchanged after treatment with the drugs The orthostatic decrease, however, was exaggerated during poldine treatment ($p < 0.001$ as compared to < 0.005) and disappeared during hyoscyamine treatment ($p < 0.20 > 0.10$) The cardiac output during exercise was unchanged on poldine treatment but was lower on hyoscyamine treatment ($p < 0.025$)

The *stroke volume* both sitting and recumbent was unchanged in the poldine-treated patients The orthostatic decrease was more pronounced than before treatment In the hyoscyamine-treated patients the stroke volume decreased in the recumbent position ($p < 0.02$) with a less pronounced orthostatic decrease No change was seen during exercise

The *peripheral resistance* was unchanged during treatment The orthostatic increase was more pronounced during poldine and disappeared during hyoscyamine

on a bicycle ergometer before (B) and during (D) long term hyoscyamine treatment in six subjects

RA		LVW		LVSW		Oxygen cons (ml/min)		Ventilation (l/min)		RQ		Oxygen A V diff	
B	D	B	D	B	D	B	D	B	D	B	D	B	D
Recumbent													
+2 0	+3 0	8 97	8 32	133 0	120 3	272 8	259 8	9 44	10 60	0 773	0 818	38 5	39 5
0 6	0 9	1 18	0 82	16 5	13 2	17 9	17 8	0 68	1 40	0 021	0 038	2 5	3 0
< 0 02	<0 01	<0 01		<0 01				<0 025				<0 02	<0 02
Sitting													
−2 8	−1 8	7 52	7 55	109 5	107 3	265 0	282 2	10 26	11 88	0 793	0 805	44 2	46 0
1 1	1 0	1 02	0 91	14 8	10 1	15 3	22 4	0 71	1 04	0 016	0 016	2 7	3 2
Exercise													
−0 5	+0 7	23 3	21 0	157 0	140 7	1 733 2	1 707 8	60 68	64 52	0 996	0 994	117 0	124 8
1 0	1 2	2 1	2 1	16 4	13 8	75 8	37 3	7 10	6 38	0 025	0 029	9 4	7 4
									<0 10				

jections of anticholinergic substances has been studied

During the first few minutes after injection of atropine intravenously an increased heart rate and cardiac output was found in recumbency (3, 4, 5, 6) In a recent study (1) methylscopolamine when given intravenously caused an increase in heart rate and decrease of stroke volume in the recumbent position but the orthostatic reactions were maintained During exercise there was attenuation of the heart rate and stroke volume changes The cardiac output was constant

The orthostatic effects of atropine on man were studied by Weissler et al (16) One to three minutes after 2 mg i v cardiac output rose 28 per cent, heart rate 69 per cent and brachial arterial mean pressure 9 per cent with the patient recumbent When tilted 60° from the horizontal *(head up)*, the cardiac output and arterial pressure were unchanged and the heart rate increased 81 per cent The orthostatic reaction of cardiac output and heart rate was thus similar to that of our poldine treated patients

Poldine being a quaternary ammonium compound is considered not to penetrate the "blood brain" barrier It has a strong antiacetylcholine activity and no ganglionic blocking activity in the doses used The circulatory effects of poldine in man have not been studied Tachycardia may, however, appear as

TABLE III Hemodynamic data during rest in the recumbent and sitting positions and during exercise Mean values, SE and P values

HR		BA_S		BA_D		BA_M		CO		SV		$\frac{BA_M}{CO}$	
B	D	B	D	B	D	B	D	B	D	B	D	B	D
Recumbent													
68 2	71 2	123 8	122 5	69 3	73 6	89 8	91 0	7 29	6 73	108.8	99 3	12 8	13.6
5 3	7 5	5 5	4 5	4 0	3 5	4 7	4 1	0 80	0 49	11 8	12 1	1 1	0 8
											<0 02		
								p<0 005	<0 20	<0 005	<0 05	<0 025	
Sitting													
70 3	71 7	120 5	119 8	70 5	72 2	88 2	88 8	6 24	6 24	91 7	91 2	15 2	15 0
6 3	7 4	6 8	5 2	3 9	5 6	5 2	5 8	0 78	0 60	12 5	12 1	1 7	1 6
Exercise													
153 2	153 7	183 0	158 5	81 7	80 7	115 2	109 8	14 78	13 98	100 5	95 3	7 92	8.00
15 9	15 1	10 9	6 8	3 7	6 4	5 9	7 0	0 98	0 98	10 2	9 8	0 51	0 59
			<0 05						<0 025				

Symbols as in table II

The blood loss of about 200 ml during the first examination was spontaneously restored until the second examination as judged from the hematocrit The hematocrit was 39 8 (S E 1 8) and 39 2 (S E 1 8) respectively at the first and second study in the hyoscyamine group, and 38 and 37 respectively in the poldine group Great care was taken to repeat the study exactly The study was made in a quiet room with a rest period between the recordings and after the catheter had been introduced, one of at least half an hour in order to minimize the influence of apprehension and the blood loss

An indication of good anticholinergic effect was dryness in the mouth Secretion studies also revealed a substantial decrease of gastric acidity during treatment with hyoscyamine and poldine This was recorded both basally and after histamine stimulation (9)

No symptoms referring to the circulatory system appeared during treatment despite the high doses compared with those usually recommended Nor were there any changes in bowel habits or micturition One patient had some visual disturbances (HK)

The circulatory changes on optimal anticholinergic treatment demonstrated in the present study are small but qualitatively different with the two different drugs This is in contrast to what has been found when the acute effect of in

Summary

1 Two anticholinergic drugs, poldine, which is claimed not to penetrate the blood brain barrier and hyoscyamine which penetrates the barrier, were given in optimal effective doses to 8 and 6 patients with peptic ulcers, respectively

2 Heart rate, brachial arterial pressures right atrial pressures dye dilution cardiac outputs and expiratory gases were determined during rest in the recumbent and the sitting position and during graded work sitting on a bicycle ergometer

3 The heart rate increased in the sitting position during poldine treatment The systolic pressure during exercise decreased during hyoscyamine as did the cardiac output The stroke volume decreased in recumbency during hyoscyamine treatment The oxygen consumptions in recumbency and during exercise decreased during poldine treatment

The orthostatic reactions were exaggerated by poldine and diminished or vanished by hyoscyamine

4 All changes were small and harmless and carried no subjective symptoms The drugs put no increased load on the circulation when given for long periods

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part of its action In the present study the heart rate increased during treatment when the subjects were sitting, but not when they were recumbent The increase of heart rate was not accompanied by increased cardiac output A greater decrease in venous return when the subjects were sitting during poldine treatment may be the mechanism responsible for this finding The mean right atrial pressure thus was 2 7 mm Hg in the recumbent position decreasing to — 3 4 mm Hg in the sitting position The corresponding values before treatment were 2 4 mm Hg and — 2 0 mm Hg

This orthostatic central venous pressure decrease during treatment was accompanied by a more pronounced drop in cardiac output, from 7 84 l/min to 6 27 l/min, the corresponding mean values before treatment being 7 28 l/min and 6 52 l/min Similar changes were found regarding the stroke volume As there were only minor variations in arterial pressures correponding changes in total peripheral resistance, left ventricular work, and stroke work also appeared

During exercise there were no changes in heart rate, cardiac output and blood pressures

The oxygen consumption decreased during rest in the recumbent position and during exercise on poldine treatment This may be due to less apprehension and greater confidence at the second study A similar decrease during exercise was observed by Robinson et al (7) about an hour after 2 mg atropine injection intramuscularly

Hyoscyamine penetrates the brain-blood barrier (2) No circulatory symptoms appeared during treatment

Hyoscyamine had no influence on heart rate, diastolic and mean arterial pressures during rest or exercise During exercise the systolic pressure and cardiac output decreased The orthostatic decrease in cardiac output was abolished during hyoscyamine treatment — an effect contrary to that of poldine Stroke volume during hyoscyamine was lower in the recumbent position and unchanged in the sitting — the orthostatic decrease of stroke volume was diminished A decrease in the stroke volume during influence of anticholinergic drugs has been demonstrated only when the heart rate increased (1)

As the arterial pressure was unchanged the abolished orthostatic reaction of cardiac output during hyoscyamine was also reflected in abolished increase in total peripheral resistance and decrease in left ventricular work and stroke work in the sitting position The orthostatic reaction of right atrial pressure was maintained In this study the influence of long term anticholinergic treatment on the circulatory system was thus mainly seen regarding the orthostatic reactions with poldine exaggerating and hyoscyamine diminishing them The present data cannot differentiate between a central nervous system effect of hyoscyamine or a different peripheral effect of the two drugs

The circulatory effects seen in this study after prolonged optimal treatment with the two anticholinergic drugs during rest and exercise were only small and did not cause any discomfort to the patients

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The Effect of a β-Adrenergic Blocking Agent (Nethalide) on Serum Lipids and Glucose in Man

By

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Recently nethalide (2 isopropyl amino-1 (2 naphthyl) ethanol hydrochloride) (I C I) was introduced as a β adrenergic receptor blocking agent It blocks myocardial adrenergic receptors (2) as well as epinephrine induced increase in serum free fatty acids (FFA) (10)

To elucidate further the mechanism of action of the drug on carbohydrate and lipid metabolism the present study, using prolonged oral administration was performed

Material and methods

Fourteen subjects 3 females and 11 males aged 26 to 64 years, were selected for the study Seven had a moderate untreated hypertension one coronary heart disease and one was obese table 1)

The subjects were given 0 1 to 0 3 g of nethalide three to four times daily for about a week table 1 the last dose two hours before study The study on nethalide treatment preceded the non treatment study in three subjects and the drug was then withheld for at least five days before the non treatment study was carried out

Investigations were performed in the morning in the post absorptive state A polyethylene catheter was placed in the brachial artery after local anaesthesia using 10—15 mg of lidocain without epinephrine

For FFA determinations performed in 6 subjects (1—6 in table I) three samples from the artery were taken during rest 10 5 minutes and 1 minute respectively before exercise on an electrically braked bicycle ergometer The exercise was started about two hours after insertion of the catheter and continued for 11 minutes Arterial samples were taken after 2 4 6 8 9 10 and 11 minutes of exercise and after exercise at 1 3 and 5 minutes with the subjects remaining resting on the bicycle

Determinations of triglycerides cholesterol phospholipids and glucose were performed on 1 or 2 samples taken during rest and on two samples during exercise

The work load was 600 kpm/min except in the 3 females (200 300 and 400 kpm/min respectively)

Blood samples were immediately cooled in ice water

Serum cholesterol was determined according to Cramér and Isaksson (4) phospholipids as described by Svanborg and Svennerholm (12) triglycerides according to Carlson

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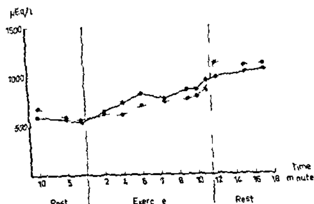


Fig 1 Serum free fatty acids before during and after exercise Mean values ● ● before nethalide ●—● during nethalide

a slight increase was noted during work The difference between the values immediately before work and the value after 8 minutes of work was significant (P < 0.02) A peak increase appeared after work The increase from the last exercise value to the value after 3 minutes of rest was highly significant (P < 0.005)

During nethalide treatment no differences were seen when changing from rest to exercise or after exercise

Serum glucose and lipids before and during nethalide treatment are listed in *table III*

Glucose concentration increased during treatment most pronouncedly during exercise (P values < 0.05 and < 0.01 respectively)

Triglyceride concentration increased on nethalide treatment significantly only during exercise (P < 0.05) No changes were observed in cholesterol and phospholipid concentrations The variations of glucose cholesterol and phospholipid concentrations before and during exercise parallelled hematocrit values

Discussion

Serum glucose concentration increased after a period of nethalide treatment with fairly high doses A similar increase was found after comparable doses of nethalide by Pilkington et al (10) in five subjects during rest

Nethalide seems to have a slight epinephrine like activity on the rat epididymal fat pad *in vitro* as far as regards increasing lipolysis (1) This suggests the possibility of an increase in glycogenolysis caused

Table II FFA mEq/l before and during nethalide treatment in six subjects Mean values and SE

	Immediately before exercise	Exercise 8 min	3 min after exercise
Before	0.557 ± 0.060	0.739 ± 0.062	1.238 ± 0.315
During	0.534 ± 0.093	0.759 ± 0.177	1.014 ± 0.190

TABLE I

Case	Diagnosis	Sex	Age (yrs)	Height (cm)	Weight (kg)	Dose nethalide $\frac{\text{Daily dose (g)}}{\text{No. of days}}$ + last dose
1	Normal subject	♂	26	186	97.5	$\frac{0.6}{2}+\frac{0.9}{4}+0.3$
2	Hypertension	♂	45	172	71.8	$\frac{0.6}{2}+\frac{0.9}{4}+0.3$
3	Sarcoidosis	♂	38	177	69.1	$\frac{0.6}{2}+\frac{0.9}{6}+0.3$
4	Hypertension	♂	47	176	64.4	$\frac{0.6}{2}+\frac{0.9}{2}+0.3$
5	Normal subject	♂	32	192	84.2	$\frac{0.3}{2}+\frac{0.6}{1}+\frac{0.9}{2}+0.3$
6	Coronary disease	♂	50	179	75.4	$\frac{0.6}{3}+\frac{0.9}{8}+0.3$
7	Hypertension	♀	43	165	73.6	$\frac{0.4}{7}+0.1$
8	Hypertension	♀	43	165	53.5	$\frac{0.4}{5}+0.1$
9	Hypertension	♂	52	175	67.2	$\frac{0.6}{5}+0.2$
10	Hypertension	♂	54	167	78.0	$\frac{0.2}{1}+\frac{0.4}{6}+0.2$
11	Hypertension	♂	64	187	86.4	$\frac{0.6}{4}+\frac{0.9}{2}+0.3$
12	Normal subject	♂	26	176	67.9	$\frac{0.4}{1}+\frac{0.6}{7}+0.2$
13	Obesity	♀	40	163	92.3	$\frac{0.4}{6}+0.2$
14	Normal subject	♂	28	182	75.9	$\frac{0.9}{6}+\frac{0.4}{1}+0.3$

(3) and FFA according to Dole (5) after purifying the heptane phase with dilute sulphuric acid and using Nile Blue as indicator. Glucose was determined on serum by a glucose oxidase method (9).

Results

The levels of FFA before, during and after exercise are demonstrated in fig. 1 and table II. Before nethalide treatment

almost all the fuel in the post absorptive state (8) The present findings might indicate a decrease in influx as well as efflux of FFA from plasma, giving a changed balance at a lower turnover level on nethalide treatment Isotope technique determinations of turnover rates, efflux and influx of FFA are needed to clarify the actual mechanism

Summary

Free fatty acids (FFA) cholesterol, phospholipids, triglycerides and glucose in serum were measured during rest and exercise before and during long term treatment with nethalide a β adrenergic receptor blocking agent

The increase in FFA during exercise and the peak increase after exercise seen before treatment disappeared during treatment The triglycerides increased during exercise and the glucose concentration increased during nethalide treatment Cholesterol and phospholipids were unchanged

Possible mechanisms for these changes are discussed

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TABLE III Serum glucose and lipids before and during treatment with nethalide Mean values and SE No of patients in brackets

	Rest	Exercise
Glucose mg% (10)		
Before	93 ± 3	96 ± 3
During	[1]98 ± 2	[2]102 ± 3
Cholesterol mg% (13)		
Before	216 ± 12	233 ± 14
During	205 ± 11	222 ± 13
Triglycerides, mM/l (13)		
Before	0 86 ± 0 12	0 78 ± 0 11
During	0 88 ± 0 09	[1]0 91 ± 0 11
Phospholipids mg% (12)		
Before	221 ± 9	243 ± 11
During	*213 ± 9*	*237 ± 11*

[1] $P < 0.05$ [2] $P < 0.01$

by the drug *In vitro* studies, furthermore, demonstrated diminished adipose tissue uptake of glucose in the presence of nethalide at rather high concentrations (1) A decreased uptake of glucose by adipose tissue might thus also contribute to the serum glucose elevation in the *present study* This may not be true with respect to other tissues, however The respiratory quotient is higher during nethalide treatment also during exercise (11), and this indicates an overall increase in carbohydrate utilization, possibly preceded by an increased overall uptake of glucose in tissues The variations of uptake rates of glucose by different tissues seem to balance each other fairly well, however, as the total uptake probably is not changed, indicated by constant disappearance rates of intravenous glucose loads in a few patients before and during nethalide treatment (unpublished observations)

The increase in serum triglyceride may be secondary to an effect of nethalide on adipose tissue This might correspond to the findings *in vitro* where nethalide promotes increased outflow of fatty acids (1), *an effect due to blocking of glucose uptake* and/or intrinsic sympaticomimetic effect of nethalide (1) Increased fatty acid outflow might increase the serum triglyceride level via esterification in the liver (7)

Isotope studies (6, 8) demonstrate increased turnover rate of FFA during exercise Havel et al *(8) found a fast increase* in efflux from plasma during exercise and a more gradual elevation of influx which explains the increased plasma FFA after the initial decrease After work *efflux fell more than influx*, leading to an increase in plasma FFA

Similar changes except for the initial decrease were observed in the *present* study, where submaximal work was performed for a comparably short time During nethalide treatment the increase during exercise as well as the concentration peak after, had disappeared This is due to a changed relationship between FFA influx and efflux Nethalide is *known to block the release (influx) of* FFA by catecholamines (1, 10), substances elevated in blood during exercise (13) The respiratory quotient increased during nethalide treatment (11) and this indicates a relative decrease in fat oxidation which otherwise comprises

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Complete Heart Block in Rheumatoid (Ankylosing) Spondylitis

By

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A total atrioventricular block is usually due to structural damage of the atrioventricular node bundle of His or bundle branches Traditionally ischaemic and hypertensive heart diseases have been considered to be the most important causative factors (15) Recent clinical (16) and histological (8) evidence however emphasizes the apparent rarity of coronary heart disease and diastolic hypertension in the etiology of total heart block Instead a patchy fibrosis of obscure origin damaging both bundle branches or bundle of His was present in the majority of patients studied by Lenègre and Moreau

Rheumatoid diseases are known to cause a variety of mostly unspecific changes in the myocardium The occurrence of partial atrioventricular block in rheumatoid arthritis (14) Reiter's syndrome (3) and rheumatoid (ankylosing) spondylitis (2, 4) is well known As far as we are aware total heart block in association with rheumatoid spondylitis has been reported so far in six patients (1, 9, 10, 12)

Because rheumatoid spondylitis as a possible etiological factor in the development of total heart block has gone largely unnoticed in cardiological discussion we consider it justifiable to report four further cases of the association of rheumatoid spondylitis and total heart block

Case reports

Case 1 A 46-year-old janitor At the age of 22 he had had swelling of the left ankle after tonsillitis During the next ten years he suffered from episodes of mild fever aching and swelling of the ankle and knee joints and aching of the lower back and interscapular area At the age of 31 the patient was admitted to a hospital because of a feeling of tightness in the chest and swelling of the interphalangeal joints of the feet The ESR was 75 mm/h The heart was clinically normal but the ECG revealed a prolonged PQ time varying between 0 35—0 40 seconds Intermittent bursts of atrial tachycardia with

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conservative treatment and occasional Stokes Adams attacks an electric cardiac pacemaker was installed after which the heart failure subsided Even after that the liver function tests showed impairment of function the bromsulphalein retention was 14 %/45 min

Comments

The patient had rheumatoid spondylitis, which had begun at the age of 30 and now involved the entire spine Thirty years after the onset of spondylitis total heart block appeared In addition the patient had probably alcoholic cirrhosis of the liver Because no other form of heart disease was apparent apart from the block it seems possible that total heart block was a manifestation of rheumatoid spondylitis affecting the heart

Case 4 A 62 year-old retired labourer The patient had been well until at the age of 45 diabetes mellitus was diagnosed and controlled with insulin treatment Three years later the patient suffered from anterior uveitis and after that recurring pain and stiffness of the lower back On admission at that time the ESR was 47 mm/h the vertebral column was roentgenologically normal and the ECG revealed a normal sinus rhythm The next thirteen years the patient lived with temporary discomfort of the spine and his diabetes well in control At the age of 61 congestive heart failure developed rapidly without symptoms or signs suggesting ischaemic or hypertensive etiology In addition some syncopal attacks occurred A total heart block with an idioventricular rhythm of 34 42/min was diagnosed and an electric pacemaker was installed with relief of symptoms At a control visit to hospital the history of backache called attention to the spine In roentgenograms both sacroiliac joints were seen to be partly ankylosed and there was bridging between thoracic vertebrae 10 and 11 The Waaler Rose and latex fixation tests were negative An additional finding was increasing proteinuria The urinary sediment and culture were normal and the serum creatinine concentration 1 7 mg % The Congo red test showed 70 % disappearance of the dye in 1 hour

Comments

The patient had diabetes mellitus and mild rheumatoid spondylitis which had begun with anterior uveitis at the exceptionally late age of 48 A total heart block appeared twelve years after the onset of spondylitis In addition, the patient probably had amyloid disease, which is occasionally known to complicate rheumatoid spondylitis Whether the patient might have amyloid deposits in his heart cannot be determined at present However, an etiological relationship between rheumatoid spondylitis and total heart block seems possible

Discussion

It is open to question whether total heart block and rheumatoid spondylitis in the above patients had anything in common other than being a coincidence An etiological relationship, however is supported by the lack of any other apparent cardiologically significant disease Further, the high incidence of the first and second degree atrioventricular block in rheumatoid spondylitis (1, 4 6 7) speaks for damage of the atrioventricular conduction system In addition pathological changes are known to occur in the heart in rheumatoid spondylitis consisting of inflammatory patches of the right atrial wall (2) and necrosis of the aortic media (11 13) which leads

a 2 I atrioventricular block were noted in addition During the next few years increasing stiffness of the lower back developed At the age of 42 destruction of both sacroiliac joints and formation of syndesmophytes in the thoracic spine were seen in roentgenograms The heart was otherwise clinically normal, but now the ECG showed a total atrioventricular block with an idioventricular rhythm of 40—60/min The Waaler-Rose test was negative The patient never had symptoms suggesting uveitis During the last four years the changes in the sacroiliac joints and thoracic spine have progressed and some squaring is seen in the roentgenograms The total heart block continues to be symptomless with an idioventricular rhythm of 40—60/min

Comments

The patient had rheumatoid spondylitis, which had begun with a transitory arthritis In ten years a first and second degree atrioventricular block developed Twenty years from the onset of the symptoms a total heart block was diagnosed In view of the lack of manifestations of other cardiac disease it seems reasonable to suppose that the disturbance of atrioventricular conduction was etiologically linked with rheumatoid spondylitis

Case 2 A 46 year old warehouse truck driver The patient had been well until at the age of 34 he began to suffer from long lasting arthritis affecting most joints of the extremities At the height of joint symptoms he developed anterior uveitis which severely damaged his right eye During the next ten years there were episodes of back pain and the spine gradually became stiff At the age of 45 the patient experienced sudden syncopal attacks and in the hospital a total heart block with an idioventricular rate of 30—40/min was diagnosed with no symptoms or signs of any other heart disease In particular, nothing to suggest ischaemic, hypertensive or rheumatic heart disease was present An electrical cardiac pacemaker was installed Later during a control visit to the out patient clinic attention was paid to the patient's stiff back In roentgenograms both sacroiliac joints were seen to be ankylosed and there was extensive bridging of the thoracic and lumbar spine

Comments

The patient had rheumatoid spondylitis which had begun with symptoms of peripheral arthritis Later anterior uveitis occurred A total heart block appeared ten years after the onset of symptoms In view of a lack of other manifest heart disease it seems probable that the rheumatoid spondylitis and the total heart block were etiologically linked

Case 3 A 67 year-old organist At the age of 17 he probably had glomerulonephritis, but otherwise he was well, until at the age of 30 he began to suffer from aching of the lower back and later of the whole spine During the next twenty years the whole spine became gradually quite stiff There was nothing in the history to suggest uveitis At the age of 60 the patient was admitted to hospital because of Asian influenza The pulse at that time was said to be 35—40 min A year later however, a regular normal sinus rhythm was seen in the ECG during an examination for life insurance At the age of 62 the patient found physical exertion progressively difficult because of shortness of breath and noticed a slow pulse of 30—40 min There was no chest pain before or during the symptoms He was admitted to hospital with increasing heart failure The physical examination revealed a moderately enlarged heart blood pressure 190/90 pulse 30—40 min and a grade 3 systolic ejection type murmur of medium pitch at the apex The ECG showed total heart block The Waaler Rose titre was 0 and the latex fixation test positive After disappointing

heart block might include rheumatoid spondylitis In any case, histological data of the atrioventricular conduction system in rheumatoid spondylitis are urgently needed

Summary

A first degree atrioventricular block in association with rheumatoid (ankylosing) spondylitis is a not uncommon finding Four patients with total heart block and rheumatoid spondylitis are described The conduction defect appeared relatively late, i e 10—30 years after the onset of spondylitis In no case was there anything to suggest ischaemic, hypertensive or other form of heart disease as the causes of total heart block On the basis of known histological changes in the heart in rheumatoid spondylitis it seems probable that an etiological relationship may exist between rheumatoid spondylitis and total heart block Considering this possibility in patients with total heart block of obscure origin more cases may come to light than the few that have been reported so far

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to dilatation of the aortic root and aortic incompetence Information of the atrioventricular conduction system in rheumatoid spondylitis is lacking

The incidence of total heart block in rheumatoid spondylitis is not to be determined reliably from the few cases reported in the literature Bernstein and Broch (1) reported total heart block in three of 190 patients with spondylitis, Ruffie and Fournie (10) in one of 150, and Suter and Steiger (12) in one of 44 patients For additional information of the incidence we studied the records of an unselected series of 97 patients with rheumatoid spondylitis in a general hospital None of them had total heart block Six patients had a PQ time of over 0 22 seconds, one of these having temporary atrial tachycardia with 3—4 1 atrioventricular block One patient had a temporary 2 1 atrioventricular block and one patient a right bundle branch block with normal PQ time Two patients had a symptomless aortic incompetence without conduction defect Thus according to the available data the incidence of total heart block in rheumatoid spondylitis seems to be somewhat less than 1 per cent Further clinical work is necessary for a more reliable approximation of the incidence

The fact that total heart block has been described in only a few patients with spondylitis, although partial atrioventricular block is fairly common, may be due to usually mild inflammatory damage of the conduction system Another possibility is that patients with total heart block may have mild or atypical rheumatoid spondylitis, which is likely to go unnoticed in face of a dramatic heart disease The history may sometimes be of little help because the early symptoms of spondylitis may be confusing Rheumatoid spondylitis may begin with peripheral arthritis or Reiter's syndrome (5, 6) and at the beginning there may be no clinical or roentgenological signs in the spine Sometimes the early symptoms suggest rheumatic fever (6, 9), although in contrast to rheumatic fever the peripheral arthritis is usually transitory and remains in the same joints for months Thoracic and girdle pain at rest and the sacroiliac syndrome are most helpful in the diagnosis of rheumatoid spondylitis The Waaler Rose test is usually negative

The appearance time of total heart block after the onset of rheumatoid spondylitis varied in our patients from ten to thirty years On the other hand patients with partial atrioventricular block and spondylitis have usually been in their forties or fifties (12), while spondylitis itself usually begins at the age of about 25 years Thus probably the inflammatory damage of the atrioventricular conduction system progresses rather slowly towards a derangement of function

The emergence within a short time of four cases of rheumatoid spondylitis with total heart block prompts us to suggest that the combination may not be very rare More cases will undoubtedly be found if the possibility of rheumatoid spondylitis is held in mind in cases of total heart block It is very interesting to speculate whether the unknown origin of fibrosis of the bundle of His and bundle branches described by Lenègre and Moreau (8) in total

heart block might include rheumatoid spondylitis. In any case histological data of the atrioventricular conduction system in rheumatoid spondylitis are urgently needed.

Summary

A first degree atrioventricular block in association with rheumatoid (ankylosing) spondylitis is a not uncommon finding. Four patients with total heart block and rheumatoid spondylitis are described. The conduction defect appeared relatively late, i.e. 10—30 years after the onset of spondylitis. In no case was there anything to suggest ischaemic, hypertensive or other form of heart disease as the causes of total heart block. On the basis of known histological changes in the heart in rheumatoid spondylitis it seems probable that an etiological relationship may exist between rheumatoid spondylitis and total heart block. Considering this possibility in patients with total heart block of obscure origin more cases may come to light than the few that have been reported so far.

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Familial Cardiomyopathies[1]

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It is an embarrassing fact that *the cause of death* in many instances of heart disease remains obscure Death is usually ascribed to a structural deviation from *normal* recognized by the physician or established by the pathologist but the immediate *causal* relationship between the existing structural defects and the acute event precipitating death is *often* doubtful or unexplained To this day the processes in cardiac muscle that *convert energy into motion* are only known in their least crucial parts and the reasons why this *process* ceases to continue or goes astray are equally incompletely understood A kidney may gradually lose its *working units* a lung may likewise blow up useful alveoli into useless emphysematous cysts and a liver may run the cirrhotic course *to its* deplorable end But *in* all these cases the slope is gradual and can be indicated by numerical values of diminishing function leading to an intoxication the final victim of which by our conventional definition of death is the heart The same course of events may be seen in progressive myocardial failure as expressed in *functional terms* (cardiac output, venous pressure etc), but there does not seem to exist any quantitative rules regarding the *degree* of myocardial hypertrophy or of stretching of muscle fibers in cardiac dilatation, which approaches and surpasses the limits of life Cardiac patients may die with normal sized hearts, with moderately sized hearts and with enormous hearts obviously, some *cardiacs* manage to live with tremendous *hearts*, while others die with much *smaller ones* There must be much more to the *qualities* of heart muscle than we know of

In the early time of major emphasis on rheumatic valvular heart disease it was taken for granted that a highly stenotic or regurgitant heart was simply "worn out" by exertion as life expired With increasing emphasis on coronary

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In this large group one will find to-day both cardiac manifestations of general disorders such as infections (bacterial, viral, protozoan etc), rheumatic fever, collagen diseases, sarcoidosis, metabolic disorders (beri beri hemochromatosis) and neuro-muscular diseases (myotonias Friedreich s ataxia etc) and apparently *isolated* diseases of the heart (25) In the latter case the initial differential diagnosis against coronary heart disease has often to be based on the patient s age or the familiar occurrence of sudden death in young persons There appears to be some well-defined isolated cardio myopathies (7—9, 15 18—24 28—30) — of which we have ourselves encountered some examples — and most of the cases presented in the literature seem to belong to a subgroup usually referred to as fa milial cardiomegaly (2, 3 11 12 13 31, 32 33) A tentative list of disease entities belonging to the main group of isolated cardiomyopathy is presented in table I

Whether or not it is proper to list side by side metabolic processes of heart muscle idiopathic muscular hyper trophy and inflammatory conditions is of course a case for argument (31) However one can also argue about the real significance of the inflammatory process It may or may not be infectious It may represent a break-down of cells for other reasons with subsequent re paratory activity

The main features that have im pressed us and aroused our diagnostic suspicion of a cardiomyopathy have been

1 *Family history* with one or several cases of sudden death or without reasonable ex planation at a comparatively young age

2 *Cardiac enlargement* not necessarily very impressive but occasionally with some thing unusual in the heart contour

3 *Electrocardiographic abnormalities* mainly in the QRS-complexes at times quite odd

TABLE I Isolated cardiomyopathy

	Diagnosis	Clinical features	Own cases
1	Glycogenosis Coris type 2	Infants	—
2	Congenital glycogenic cardiac tumor	Children	—
3	Endo-myocardial fibrosis	Constrictive cardiac failure	—
4	Primary amyloidosis	Constrictive cardiac failure Often low voltage	—
5	Asymmetrical cardiac hyper trophy	Familial Obstructive cardiac failure	D (?)
6a	Familial cardiomegaly	Familial Congestive cardiac failure Adams Stokes attacks Hyper trophy — ECG No signs of inflammation at autopsy	L. SU (?)
6b	Familial myocarditis?	Familial congestive cardiac failure Signs of in flammation at autopsy	F? SN?
7	Chronic pernicious myocarditis	Congestive cardiac failure Sudden death Signs of chronic interstitial myocarditis at autopsy	—

heart disease, diminished contractile strength was assumed to accompany the scarring of the affected heart muscle In the acute infarct, myocardial rupture or "electric instability" in boundary zones might explain instantaneous death

However, *rare, curious* and remarkable cardiac diseases have remained as thought-provoking enigmas They have not been easily fitted into current nosology, and both etiology and cause of death — often a sudden death — have remained in the dark Besides the myocardial disorders associated with some familial neuro-muscular dystrophies (5, 6) which have been known for a long time, and acute myocarditis of unidentified origin (16, 17), attention has lately been focussed upon the various forms of endo-myocardial disease observed mostly in infants and in some *tropic areas,* as *well* as *upon* some capricious conditions, designated as 'cardiomyopathies", characterized by cardiac enlargement and a tendency to sudden death, and with a peculiar inclination to run in families

A primary task in the acquisition of new medical knowledge is the accumulation and sorting of relevant observations, the breaking up of erroneously combined entities and attempts to find common denominators for *recombination of units* Among the most important areas for clinical cardiology to-day is that of medical genetics, and this applies equally to vast disease-groups, like coronary heart disease and hypertension, where the task is as difficult as it is important, and to more rare conditions such as cardiomyopathies, in which genetic factors might be more easily *discovered* and in which also other clues to the riddles of myocardial function and dysfunction might be found In the present paper, instances of "cardiomyopathies" will be reported, in which the clinical features, or the family history, or both, are considered sufficiently unusual to warrant presentation

Papers dealing with cardiomyopathies are becoming more frequent in later years Goodwin et al (14) have defined the concept of cardiomyopathy as 'a subacute or chronic disorder of heart muscle of unknown or obscure etiology, often with associated endocardial and sometimes with pericardial involvement, but not atherosclerotic in origin" Another definition is given by Robin (25) 'A broad group of diseases of diverse etiology that specifically involve the myocardium to produce abnormalities *of structure, abnormalities of function,* or both The end result of many of these disease processes may be the development of myocardial fibrosis'

In a way, these statements represent the acceptance of old truths, recently forgotten or distrusted The situation is similar to the revival of the diagnosis of mitral regurgitation, which because of previous abuse became so frowned at that few people dared to suggest it, *until the cardiac surgeons* could prove that there were such cases To-day, we must accept that there is something besides coronary heart disease which damages heart muscle Some of the chronic myocarditis" of the pre-coronary days actually were chronic myocarditis It is now to be found as a subgroup under the new heading of *cardiomyopathies*

and occas onally premature ventricular beats are observed

The pat ent has been exam ned by means of left heart catheterizat on and the systol c pressure in the left ventricle was found to be equal to that in the aorta Pulse tracings were also recorded from the right carot d artery and cons dered to be normal Three ngl tuded ang ocard ograms and one card o-aortogram have been performed (Dr H Arvidsson) (Fig 4) No abnormal t es were found n the atr a whereas the lumen of the right ventr le was found to be blocked by the th ck interventricular septum The left ventricle is greatly deformed by a tumor like mass wh ch extends into the lumen ch efly from the lateral and posterior card ac wall and in some places measures 5 cm The trabecular muscles are abnormally coarse and partl dislocated The aort c conus aort al es and aorta ascendens are normal The r ght coronary artery is normal whereas the left coronary artery is twice as wide as normal the c rcumflex branch more so than he anter or descend ng The per card um s normal

On the bas s of these f ndings the d agnos s of a rl abdomyoma at one time was cons dered most probable In the light of our present exper ence we are nclined to label it asymmetric l c rdiac hypertrophy

No 22 Male ch ld of 21 Born 6 weeks prematurel D ed af er one day n resp ra r fic ency We ght 2 100 g Autops y Dr Sumeg showed a heart cons dered to be somewhat enlarged with slight hyper rophy of the right ventricle The tricusp d al e showed some m n mal red verrucous excrescences The lungs showed atelectas s and early pne mon changes M croscop c exam na on of the myocard um and l er was non nforma e

The mother no 39 father no 31 and brother no 21 of 22 have been exam ned with regard to poss ble heart d sease The father has had a moderate hypertens on s nce 1934 The heart showed physical s gn of some enlarge

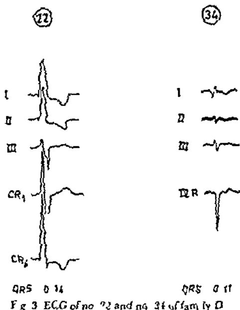


Fig 3 ECG of no 22 and no 34 of family D


Fig 4 Cardioaortogram of no 22 of family D The arrows indicate the contour of the left ventricular wall

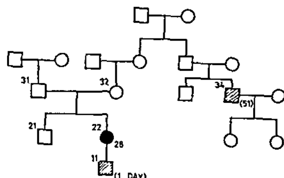


Fig 1 Pedigree of family D

☐ male ○ female ■ definite disease ☐ possible disease Figure above ☐ ○ = pedigree no Figures below indicate age at examination or death (in brackets)



Fig 2 Chest X ray of no 22 of family D

in appearance sometimes within accepted timelimits but nevertheless unusual (WPW, bundle branch block and other intraventricular conduction disturbances)

4 *Clinical course,* sometimes even with gross structural abnormalities no or very little subjective symtoms, in other cases a pernicious almost therapy resistant cardiac failure — occasionally sudden death out of a clear sky

When such cases are being autopsied, the average report contains normal heart valves, normal coronary arteries, myocardial hypertrophy, patchy myocardial fibrosis and not infrequently scattered signs of an acute inflammatory process In some instances a note is made of a "hypoplastic" aorta

We have had occasion to study patients belonging to five different families, of whom an account will be given in the following case reports

Family D (fig 1)

No 22 Female, 28 years old Mumps and bronchial asthma in childhood, otherwise healthy At routine school examination, her heart was considered enlarged At that time she had no subjective symtoms other than mild dyspnea on exertion In later years she has experienced some inconstant precordial pain of mild degree She is married and works as a secretary At age 23 she gave birth to a child (No 11), 6 weeks before term The child died, and she has not become pregnant again

After the first diagnosis of cardiac enlargement, the patient has been extensively examined, including cardiac catheterization and repeated angiocardiograms The findings are, briefly A well developed young woman with no signs of cardiac incompensation *Slight epicanthus* Heart moderately enlarged to the left with broad and lifting apex beat A rather harsh systolic murmur, grade 4 is heard with a maximum over the 4th left intercostal space No diastolic murmur Regular rhythm Blood pressure (both arms) 110/60, (both legs) 160/90 The X ray over the last ten years (fig 2) has shown an enlargement predominantly of the left ventricle, the heart volume being calculated to 1,130 ml, corresponding to 720 ml/sq m body surface The great vessels and the lungs show nothing abnormal The ECG (fig 3) indicates a tremendous left ventricular hypertrophy with QRS-complexes of 4 5 mV amplitude (in lead I) and a duration of 0 14 seconds, showing a fair degree of notching on both ascendent and descendent limbs and followed by inverted T s The P—Q interval is short 0 05—0 06 seconds,

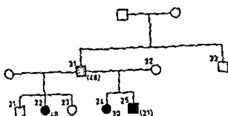


Fig 6 Pedigree of family L. Symbols as in fig 1

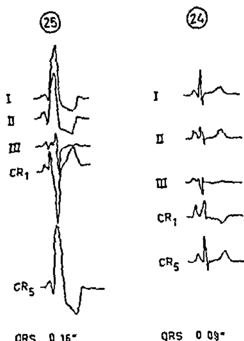


Fig 8 ECG of no 24 and no 25 of family L



Fig 7 Chest X ray of no 25 of family L.

ventricular septal wall was a fibrotic area Microscopical examination revealed fibrosis and hypertrophy in the myocardium Because of vacuolization of myofibrils a suspicion of glycogenosis was entertained This has however been refuted by Ockerman and Berlin (34) As this case remains obscure we have examined or obtained information on the nearest relatives[1]

No 24 Female 30 years old No signs or symptoms of heart disease No pathological findings at physical examination apart from a blood pressure of 145/110 Chest X ray (fig 9) normal ECG (fig 8) pathological with remarkable tall P waves particularly corresponding to the right atrium Prolonged ventricular activation time and ST T-changes over the right ventricle

No 32 Female 59 years old Mother of 24 and 25 She has had diabetes for the last ten years Otherwise nothing remarkable



Fig 9 Chest X ray of no 24 of family L

from her heart neither subjectively nor objectively X ray and ECG both normal

No 31 Male father of 21 to 25 Died suddenly at age 46 after having had dyspnea for some years A diagnosis of cardiac enlargement had been made five years prior to his death

[1] We thank Dr S. O. Berlin for information on the members 21 23 of this family



Fig 5 Chest X ray of no 34 of family D

ment, but was otherwise normal The blood pressure was 170/100 The mother had neither symptoms nor signs of any heart disease

The brother had normal physical findings His ECG revealed a minor intraventricular conduction disturbance

The grandparents all died in old age However, a cousin of the mother (no 34) died from heart disease aged 51

No 34 Male 51 years old He had not had rheumatic fever, but at age 20 he was said to have had some proteinuria for a while At age 36 hypertension was diagnosed and at age 40 he was admitted to a local hospital, where he was diagnosed as having chronic myocarditis At that time blood pressure values of 230/120 were noted In later hospital admissions his blood pressure was lower, 200/100 The diagnosis was then benign essential hypertension with progressive cardiac failure The kidney function seems to have been normal with little or no albumen normal casts specific gravities to 1 030 and a normal NPN up to the final stage The physical examination revealed an enlarged heart with displaced apex beat A systolic murmur with maximum over the lower precordium was noted Auricular fibrillation was noted during the last ten years and in addition QRS was widened (0 12 sec) with a very deep Q_1 (fig 3) The X ray films (fig 5) showed a tremendous, progressive enlargement, from 840 ml sq m body surface in 1946 to 1700 ml sq m body surface in 1955 and 3,000 ml/sq m. body surface in 1956 He died with intractable heart failure a year later Autopsy was, unfortunately, not performed

Whether this case has a common denominator with case 22 is hard to state The place of the hypertension in the picture is intriguing Despite the possibility of an initial acute glomerulonephritis, there is little evidence of chronic renal damage with secondary hypertension

In summary, the family D presents one young female patient with asymmetrical cardiac hypertrophy, her only child, prematurely born, and dying with signs of heart disease, and a cousin of the patient's mother with a most remarkable cardiomegaly

Family L (fig 6)

No 25 Male, 20 years old A brief case report on this patient has been given earlier (10) For about five years he had had attacks of tachycardia, provoked by exercise and emotion They ended abruptly and were sometimes followed by syncope At physical examination he showed no signs of cardiac failure An ejection murmur over the left I I_2 was observed Blood pressure 130/80 X ray (fig 7) showed a moderately enlarged heart 580 ml sq m body surface ECG fig 8) short P—R interval, QRS sometimes normal sometimes of bundle branch type — probably a case of pre-excitation (35) Later in the course the patient developed complete heart block with Stokes Adams syndrome requiring implantation of a pacemaker One week after operation ventricular fibrillation and death *Autopsy* (Dr B Ivemark) showed a heart of 825 g Valves coronary arteries and aorta normal In the

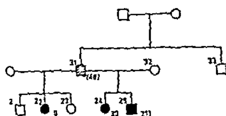


Fig 6 Pedigree of family L. Symbols as in fig 1



Fig 7 Chest X ray of no 25 of family L.

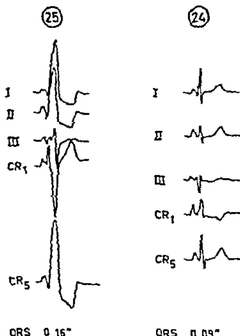


Fig 8 ECG of no. 24 and no 25 of family L.

ventricular septal wall was a fibrotic area. Microscopical examination revealed fibrosis and hypertrophy in the myocardium Because of vacuolization of myofibrils a suspicion of glycogenosis was entertained This has, however been refuted by Öckerman and Berlin (54) As this case remains obscure we have examined or obtained information on the nearest relatives.[1]

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No 32 Female 59 years old Mother of 24 and 25 She has had diabetes for the last ten years Otherwise nothing remarkable from her heart, neither subjectively nor objectively X ray and ECG both normal

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Fig 9 Chest X ray of no 24 of family L.

[1] We thank Dr S O Berlin for information on two members (?1 2?) of this family



Fig 5 Chest X ray of no 34 of family D

ment, but was otherwise normal The blood pressure was 170/100 The mother had neither symptoms nor signs of any heart disease

The brother had normal physical findings His ECG revealed a minor intraventricular conduction disturbance

The grandparents all died in old age However, a cousin of the mother (no 34) died from heart disease aged 51

No 34 Male, 51 years old He had not had rheumatic fever, but at age 20 he was said to have had some proteinuria for a while At age 36 hypertension was diagnosed and at age 40 he was admitted to a local hospital, where he was diagnosed as having chronic myocarditis At that time blood pressure values of 230/120 were noted In later hospital admissions, his blood pressure was lower, 200/100 The diagnosis was then benign, essential hypertension with progressive cardiac failure The kidney function seems to have been normal, with little or no albumen normal casts specific gravities to 1,030 and a normal NPN up to the final stage The physical examination revealed an enlarged heart with displaced apex beat A systolic murmur with maximum over the lower precordium was noted Auricular fibrillation was noted during the last ten years and, in addition, QRS was widened (0 12 sec) with a very deep Q_1 (fig 3) The X-ray films (fig 5) showed a tremendous, progressive enlargement, from 840 ml sq m body surface in 1946 to 1700 ml/sq m body surface in 1955 and 3,000 ml/sq m body surface in 1956 He died with intractable heart failure a year later Autopsy was unfortunately, not performed

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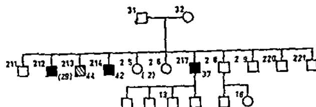


Fig 10 Ped gree of fam ly SU Symbols as n fig 1

No 214 Male 42 years old has had angina of effort since 4 years and had been hosp tal zed with susp cion of myocardial nfarct on or some hered tary card ac disease a year ago Re exam ned by us Nothing abnormal at phys cal *exam nat on* Blood pressure 160 95 The ECG (f g 12) sho ed tall QRS complexes and ST T abnormal t es correspond ng to the left ventricle Card ac catheterizat on (right and left) showed *noth ng abnormal* X ray (fig 13) angiocard ography and coronary ang ography showed normal cond t ons Cholesterol 356 mg % and normal i v glucose tolerance test

No 215 Female 12 years old Qu te healthy unt l f nal illness After ha ng felt t red for one week she became unconsc ous during the n ght and exp red the next *morn ng* Exam nat on of her urine is sa d to ha e shown mass ve glycosur a

No 216 Female 39 years old H story w h some palp tation The thyro d somewhat enlarged Phys cal find ngs chest X ray and elect ocard ogram normal

No 218 Male 35 years old Apart from s ght thyro d enlargement noth ng abnormal subject vely and object vely

No 219 Male 33 years old D abetes s nce age 20 No heart troubles X ray shows normal heart s ze ECG QRS-durat on 0 12 sec

No 16 (rl 8 years old Much more t red than o her hild en w h ph s cal exerc se No s gns of card ac enlargement Soft s s ol c murmur grade II along the left s ernal border Blood pressure 140 85 X ray w tho t re narks ECG sl ght notch ng in V o herw se normal

No 13 Boy 11 years old Accord ng to nforma on from h s local phys c an he has



Fig 11 Chest X ray of no 217 of family SU

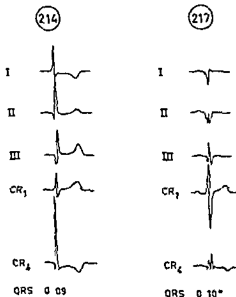


Fig 12 ECG of no 217 and no 214 of fam ly SU

TABLE II Familial cardiomegaly

	Fam L			Fam SU		
Clinical features	22	24	25	212	214	217
Progressive cardiac failure		—	—		—	—
Cardiac enlargement	+	—	+	+	—	+
Serious arrhythmia		—	+		—	—
Hypertrophy on ECG	+	+	+		+	+
Early sudden death			+	+		
At autopsy						
Left (right) ventricular hypertrophy			+			
Signs of inflammation			—			

No 33 Male, 68 years old brother of 31, has refused examination but a chest X ray three years ago has showed nothing abnormal with his heart

No 21 Male 41 years old, subjectively and objectively normal including X ray and ECG (4)

No 22 Female, 40 years old, fainting spells the last year ECG abnormal (4)

No 23 Female 35 years old subjectively and objectively normal including X-ray and ECG

This family would fit the prevailing criteria for familial cardiomegaly (Stokes Adams attacks and cardiac hypertrophy at young ages and no signs of inflammation at autopsy) (table II) The ECGs indicate, that a survey of patients who present the Wolff Parkinson-White syndrome ("pre-excitation" (35)) might bring to light more families of this kind, and we are at present exploring this possibility

Family SU (fig 10)

No 217 Male, 37 years old This man had suffered from angina of effort for 7 years, sometimes accompanied by dyspnea palpitation and nausea When he was seen by us there were no signs of cardiac failure His physical findings were equivocal Blood pressure 130/85 X ray (fig 11) enlargement particularly of the left ventricle Heart volume 700 ml/sq m ECG (fig 12) right axis deviation QRS complexes deformed in lead I, II and CR_{1-} T negative in I II and CR_{4-7} During work T-waves of the left heart become temporarily positive Exercise tolerance otherwise without remark and no pain Right heart catheterization showed only slight signs of myocardial insufficiency of the left ventricle, which was improved after intravenous digitalization Coronary angiograms showed obstructive changes at a distance of 7 cm from the origin of the right coronary artery, with collaterals Cholesterol 236 mg % I v glucose tolerance test normal

The family history revealed several instances of early heart disease, and for this reason, other members of the family were also examined

No 211 Male 48 years old Subjectively and objectively no cardiac abnormality Blood pressure 160/90 X ray and ECG normal Some thyroid enlargement without signs of disease

No 212 Male 29 years old Sudden death — had some years before been told he had cardiac enlargement No autopsy

No 213 Male 44 years old No subjective symptoms of heart disease Harsh systolic murmur grade II over 2—3 left intercostal space Blood pressure 150/90 X ray normal ECG diphasic T wave in lead CR_4 otherwise normal

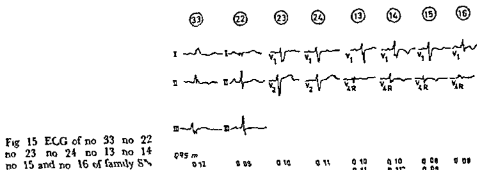


Fig 15 ECG of no 33 no 22 no 23 no 24 no 13 no 14 no 15 and no 16 of family S

one brother and one sister had died suddenly, and that the father of the patient had died from a stroke, while the mother had suffered from heart disease Medical information on these relatives were therefore obtained and analyzed[1]

No 22 Female 25 years old This patient was first examined by the family physician (who was also in charge of 25 and 33) at age 13 because of discomfort on exercise There were sore throats and otitis but no rheumatic fever in the history Apart from an accentuated P_2 no cardiac abnormalities were recorded At age 15 an X ray of the chest was taken and the heart considered somewhat large (no measurements) At this time the patient had no symptoms At age 20 there were still no symptoms and the patient engaged in tennis and square-dancing although with some dyspnea However the following year an enlargement of the heart to the right was noticed and at fluoroscopy the left auricle was said to be enlarged A soft systolic murmur over the whole cardiac area was observed The patient was given digitalis and some restriction of her activity was recommended At age 24 she was again seen by her family doctor At that time she is said to have complained of some dyspnea and palpitation At fluoroscopy the heart was increased with a triangular shape and rounded left contour Auscultation was said to have revealed a presystolic and systolic murmur, maximal at the apex and towards the third intercostal space medially The blood pressure was 135/85 The *ECG* (fig 15) showed somewhat high P waves, a splitting of QRS in lead I and a notched R in lead III

The following year at age 25 she was seen by an experienced cardiologist in Stockholm who found no increase of the apex beat Apical systolic murmur, with maximum in the 3rd left intercostal space, questionable diastolic murmur, P_2 accentuated Regular rhythm Blood pressure (right arm) 140/80 The X ray showed a relative volume of 465 ml/sq m body surface The left ventricle was enlarged and the right ventricle also was bulging The diagnosis of mitral regurgitation was given Lungs and liver were normal There was no edema Subjectively the patient reported some breathlessness and some nocturnal anxiety, both capricious in their occurrence

She was seen by the cardiologist five months later apparently in a fairly good shape and very busy as a social worker Her dyspnea was improved by digitoxin One week later during a quiet conversation over a cup of tea she fell off the chair and was dead in a matter of seconds

Autopsy (Dr I Peterzén) showed a heart of 675 g The thickness of the left ventricular wall was 20 mm that of the right ventricle 7 mm Both atrial walls were also thickened Nothing abnormal was found

[1] We thank Dr R. Johanson Dr B Johansson and Prof J Tillgren for information of some of these patients



Fig 13 Chest X-ray of no 214 of family SU

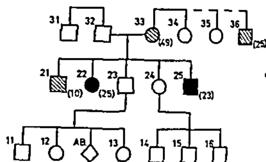


Fig 14 Pedigree of family SN Symbols as in fig 1

had a rather harsh systolic murmur as in mitral lesions' Chest X-ray without remark

No 31 Male, 60 years old, father of 211—221 Died from cerebral hemorrhage after many years of heart disease

No 32 Female 71 years old, mother of 211—221 She has auricular fibrillation since about ten years and an enormous goiter

In this family, heart disease of an unusual type — familial cardiomegaly ? (table II) — occurs together with diabetes and (non-toxic, endemic) goiter — the latter two diseases mainly in members not afflicted with heart disease It is tempting to believe in a genetic factor here

Family SN (fig 14)

No 25 Male, 23 years old Scarlet fever with otitis at age 6 At age 17 hospitalized with an acute febrile infection and possibly a mild leftsided pleurisy Otherwise no known diseases, and no pathological heart findings at physical examination or X-ray of the chest at ages 8, 11 and 17 respectively No ECG recorded

Some time prior to his death, he visited a doctor, whose name he never disclosed and was informed that he had an enlarged heart and only six months to live He did not change his way of life and continued to take part in physical exercise, apparently without discomfort

One evening, in the midst of strenuous square dancing, he fell down on the floor and expired in a short time Attempts at revival were unsuccessful *Autopsy* (Prof H Sjövall) showed a heart weighing 680 g the left ventricle being particularly enlarged The left ventricular wall was 25 mm and the right 7 mm in diameter No abnormality of valves or coronary arteries In the middle of the septum a white scar of 3 mm diameter was observed The liver weighed 2,200 g and the spleen, which was enlarged, 230 g *Microscopical* examination of the myocardium revealed a spotty fibrous thickening of the endocardium most evident in the upper part of the septum Some of the trabeculae of the left ventricle were fused together In the myocardium there were old fibrous scars both perivascularly and extending in between the muscle fibers In addition there were signs of an acute inflammatory process, characterized by small perivascular granulomas consisting of lymphocytes, histiocytes and eosinophil leucocytes The cause of death was considered to be chronic myocarditis, with acute exacerbation

The circumstances in this case warranted a further inquiry into a possible etiologic factor It was then found that

day *Autopsy* (Prof H Sjovall) showed a heart of 375 g Myocardium of normal thickness and without fibrous scars Valves and coronary arteries normal only slight atheromatosis of the aorta The lungs showed small bronchopneumoniae *Skull and brain* showed a fracture of the skull and basis of the cranium with rupture of sinus sphenoidalis subarachnoidal and subdural bleeding and contusion of the left frontal and temporal lobes

The family doctor has noted that the patient s wife had asked whether the accident might have been *caused* by an attack of unconsciousness This would go well with the description of the event and she might also have had knowledge of previous episodes The case remains obscure However the autopsy findings of the heart were normal

No 33 Female 49 years of age mother of 21—25 According to the family physician heart disease was diagnosed at age 17 without previous history of rheumatic fever However she had five pregnancies without complications At age 42 she was examined by the aforementioned doctor with no abnormal findings Chest X ray two years later showed moderate cardiac enlargement with a round left contour The following year palpitations were noted The heart was considered moderately enlarged to the left and some extrasystoles were observed She was then hospitalized in connection with an enterocolitis and it is remarked in the hospital record that she had some voussure but no abnormal physical findings X ray the heart was enlarged *particularly the left ventricle* No bulging of the left atrium Pulsations somewhat small but rhythmical An ECG (fig 35) showed what appears to be a left bundle branch block The following year she had an extirpation of the uterus without complications At the age of 49 she had a bronchitis on which occasion some extrasystoles were again noted Her blood pressure was 120 80 She was digitalized and felt better Three weeks later the patient experienced a right-sided paresis with aphasia She was treated at home and expired after three weeks No autopsy was performed The family physician issued a death certificate on organic heart disease (vitium org cordis) In the whole of this history there is little evidence of mitral stenosis which otherwise might have given rise to cerebral embolism

No 34 Female died at the age of 6 from acute pneumonia following whooping cough Sister of 33

No 35 Female died at the age of 12 from scarlet fever Half sister of 33

No 36 Male died at the age of 25 Half-brother of 33 Disappeared during swimming and never found again

Fairly extensive data on the age at death of the parents, grand parents, great grand parents etc of 32 and 33 exist Both parents and grand parents, however, lived to a high age, wi h the exception of the parents of the mother of 32 Information on the older genera tion in the ancestry of 32 shows no consistently low age of death except for some women, of whom the causes of death were given as hectic' (= tuber culosis) childbirth' and miscarriage

The family SV thus presents three instances of sudden death in childhood or young adulthood in five children, two of whom were autopsied and presented an obscure cardiomegaly, which appears to belong within the group of cardiomyopathies Although the father of the children al o died abruptly at an early age, the autopsy does not give evidence that he suffered from a similar condition The mother, on the other hand, apparently had a heart disease which might well belong to the same category as that of the children although she managed to survive longer The diagnosis of heart disease had been made in her adoles-

on the valves or coronary arteries, and the myocardium had, macroscopically, a normal appearance without fibrous scars The pulmonary artery was normal, whereas the aorta from the site of the origin of the carotid arteries and further, was reduced in size, admitting only one finger There were no signs of atherosclerosis Lungs, liver and spleen showed no abnormalities No microscopic examination was performed

In the pathologist's opinion, the deformity of the aorta was considered to explain the enlargement of the heart and the subsequent death This is highly questionable in the light of later experience with coarctation of the aorta An aorta admitting one finger should give no hypertension and no enlargement of the heart It is, instead quite probable that the cause of the cardiac enlargement, and of the sudden death resided in the myocardium itself

No 21 Boy, 10 years old The only information on this boy, apart from the death notice, derives from his only surviving brother (23), who at the time of his elder brother's death was only 5 years old The two were bathing in a small lake The elder brother was poling a raft on the lake and suddenly fell off the raft without screaming or making any sign He had learnt to swim, and he was found dead at a waterdepth of only 1 meter Attempts at rescussitation were unsuccessful No autopsy was performed

No 23 Male, 40 years old There is no history of cardiac symptoms or disability Physical findings are normal Blood pressure 130/80 X-ray normal configuration Heart volume 380 ml/sq m body surface ECG (fig 15) slight notching of S in CR_1, V_1, V_2 and aVF otherwise normal He has three children In addition, there has been one stillbirth

No 11 Boy, 14 years old, son of 23 No health troubles Physical findings normal Blood pressure 125/90 X ray nothing abnormal Heart volume 380 ml/sq m body surface ECG slight notching of R and S in V_1-V_4 and aVF, otherwise normal This boy has rosy cheeks and resembles 21 and 25 in appearance

No 12 Girl, 13 years old, daughter of 23 Never sick Physical findings normal Blood pressure 130/80 X ray Nothing abnormal Heart volume 310 ml/sq m body surface ECG slight notching of R in V_4 V_5 and aVF, otherwise normal

No 13 Girl, 5 years old daughter of 23 Imbecile No apparent congenital deformities Heart physical findings normal X ray the heart possibly somewhat enlarged (320 ml), but no typical malformation ECG (fig 15) fairly wide splitting of S in V leads and in a aVF, otherwise normal

No 24 Female, 36 years old No signs or symptoms of cardiac disease, or congenital malformations Physical findings normal Apical systolic murmur, grade 2 Blood pressure 120/80 No sign of cardiac enlargement at X ray ECG (fig 15) slight slurring of S in V otherwise nothing abnormal She has three children

No 14 Boy, 8 years old Son of 24 No signs or symptoms of cardiac disease or congenital malformations Physical findings normal Blood pressure 110/65 Chest X ray normal ECG (fig 15) fairly wide splitting of S in V_1 and V_{4R}, otherwise normal

No 15 Boy, 6 years old Son of 24 No signs or symptoms of heart disease or congenital malformations Slight systolic murmur grade 2, maximal near the left sternal border Blood pressure 105/75 Chest X ray normal ECG (fig 15) slight slurring of S in V_1 V_{4P} and aVL, otherwise normal

No 16 Boy 3 years old Son of 24 No signs or symptoms of cardiac disease or congenital malformations Physical findings normal Blood pressure 95/65 Chest X ray normal ECG (fig 15) slight notching of R in V_1 and V_{4R} otherwise normal

No 32 Male 48 years old, father of 21—25 Nothing known about previous illness One evening standing on the street quietly talking to a friend, he fell backwards without warning and was immediately unconscious Was immediately brought into hospital where the pulse is recorded to have been 80 Woke up, with aphasia Blood pressure 150/80 The patient expired on the fourth

leaned toward the former one, because of the family history

No 32 Female, 52 years old Mother of 21 This patient has been treated in another hospital[1] some months prior to her death for symptoms of cardiac failure cyanosis, dyspnea and left side pleural effusion At *autopsy* the heart weighed 500 g and contained 4 thrombi Cardiac valves and coronary arteries were normal There was considerable myocardial fibrosis A diagnosis of myocardial degeneration was made

No 23 Male 47 years old brother of 21 Alcoholic, with no signs of cardiac abnormality X ray and ECG normal

No 22 Male 54 years old former husband of 21 was found dead in his home some weeks after the death of 21 *Autopsy* revealed an acute coronary thrombosis

No 13 Male, 16 years old son of 21 and 22 This boy was brought to our department less than a week before his mother died At that time he was desperately ill with severe cardiac failure cyanotic dyspneic with pulsus alternans low blood pressure and almost no measurable cardiac output (dye dilution technique) Placed on steroids he recovered dramatically but for six months it has not been possible to withdraw the steroid medication without return to severe failure (see addendum p 423)

The medical history revealed Frequent throat infections in childhood, tonsillectomy performed three years ago One year before admission precordial pain which was considered nervous Some months prior to admission tachycardia dyspnea perspiration Physical examination cyanosis dyspnea Soft systolic murmur grade II maximal over the fourth left intercostal space P_2 accentuated Pulsus alternans Blood pressure 110 80 X ray (fig 19) considerable cardiac enlargement varying between 600 and 800 ml sq m with no typical silhouette Small pulsations increased pulmonary vascular markings Possibly small aorta ECG (fig 18) QRS 0 09—0 10 sec Minor signs

[1] We thank Dr O Forssman and Dr H Krook for information on this and the following patient



Fig 19 Chest X ray of no 13 of family F



Fig 20 Chest X ray of no 11 of family F

of intraventricular disturbance ST T abnormalities possibly due to digitalis Bacteriological virological and serological studies (incl tuberculosis toxoplasma histoplasma ornithosis Coxsackie Weil Widal) gave no evidence of any infectious etiology

No 11 Female 29 years old daughter of 21 Operated on for toxic goiter Since then hypothyroid compensated by thyroid medication No cardiac symptoms subjectively At physical examination a systolic murmur,

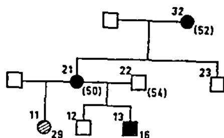


Fig 16 Pedigree of family F Symbols as in fig 1



Fig 17 Chest X ray of no 21 of family F

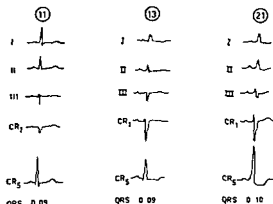


Fig 18 ECG of no 11 no 13 and no 21 of family F

cence Her two sisters died in childhood, and her halfbrother — like her eldest son — drowned at age 27

The surviving two members of the family and their children have been examined No definite cardiac abnormalities have been revealed It may be of some interest, however, that mild signs of intraventricular conduction disturbances occur in some of the electrocardiograms Marked conduction abnormalities were seen in the electrocardiograms of two of the above family members with heart disease (the mother and the daughter)

Family F (fig 16)

No 21 Female, 49 years old 2 1/2 years before death dyspnea and fatigue at exertion At that time the heart was enlarged (580 ml/sq m) She was given digitalis, but responded with a very narrow margin of toxicity Six months later temporary nocturnal cardiac asthma, possibly in connection with some upper respiratory infection After an interval of one year recurrence of symptoms She presented with some cyanosis and dyspnea but otherwise no signs of cardiac failure Physical examination revealed a systolic murmur, grade II III, over the *second third left intercostal area* The second pulmonary sound was accentuated X ray (fig 17) moderate enlargement, 520 ml/sq m ECG (fig 18) ST-T-depressions possibly due to digitalis and intraventricular contraction disturbances Management with digitalis and diuretics improved her condition but the response was somewhat unpredictable *A few months later, shortly* after having returned from a brief stay in the hospital she was found dead upon her bed *Autopsy* (Dr B Falconer) showed a heart of 570 g The valvular apparatus and the coronary arteries were normal The myocardium was without macroscopic fibrosis but microscopically (Dr H H Nordenstam) interstitial *fibrosis was found, and in scattered areas* also interstitial infiltration or lymphocytic cells

In this case, our differential diagnosis ante mortem was between cardiomyopathy and coronary artery disease We

knowledge of unusual clinical syndromes might give important clues to the discovery also of basic mechanisms of disease In this paper, after a brief survey of pertinent literature five families with probable cardiomyopathies are reported in some detail and some problems of classification are discussed

Addendum

The patient no 13 of family F died four months after submission of this paper from progressive cardiac failure despite treatment with steroids digitalis and diuretics The *autopsy* (Dr H H Nordenstam) revealed The heart weighed 790 g thus generally enlarged. The valves and coronary arteries were normal Microscopically marked perivascular fibrosis was found and in scattered areas also inflammatory infiltrations

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TABLE III *Familial myocarditis*

	Fam F			Fam SN	
Clinical features	*13*	*21*	*32*	*22*	*25*
Progressive cardiac failure	+	+	+	+	−
Cardiac enlargement	+	+	+	+	+
Serious arrhythmia	−	−			
Hypertrophy on ECG	−	−		−	
Early sudden death	+	+	+	+	+
At autopsy Left (right) ventricular hypertrophy	+	+	+	+	+
Signs of "inflammation"	+	+	+		+

grade III, was observed maximal at the fourth left intercostal space Blood pressure 120/75 X-ray (fig 20) moderately enlarged heart, 490 ml/sq m without any typical silhouette ECG (fig 18) normal

No 12 Male, 25 years old, son of 21 Subjectively and objectively normal Chest X ray and ECG without remarks

We have deliberately ventured to classify this family as "familial myocarditis" (table III) We have not been able to pinpoint any agent responsible for this unusual group of cases of *severe* cardiac failure "Acute myocarditis" is often preceded by a non-specific upper respiratory infection and in many instances it runs its *downhill* course, accompanied by equivocal and non informative laboratory data This, in a way, is how some viruses behave

As already stated, the deeper significance of the pathologist's findings of "inflammatory" signs remains obscure *But when one encounters — like in the* families SN and F — a combination of cardiac hypertrophy with signs of old and recent "myocarditis", and when one can establish what looks as a temporal relationship as concerns acute deterioration in a mother and a son, one cannot help asking How long can a *virus live in the myocardium* (or elsewhere)? At the same time as no 13 *of family F, another boy, age 16* was hospitalized here because of an acute peri myocarditis with a protracted course A penetration of the family history revealed that the boy's mother had been hospitalized two years before because of an acute *myocarditis* However, she seems now to have recovered completely There is evidence that the hepatitis *virus may survive close to twenty years* in some patients Can myocarditis be *transmitted like virus transmitted tumors*? Is there some defect in the myocardium of some people, which makes *them particularly* sensitive to the activation of a virus? Or can it be an autoimmune response of some kind?

Summary

In recent years the occurrence of obscure myocardial disease in families has been increasingly reported in the medical literature Considering that we know less about the pathophysiology and *biochemistry of cardiac muscle* and its failure than we do of many other structures and mechanisms in circulatory *disorders it may well be that a* better

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Circulation in Healthy Old Men, Studied by Right Heart Catheterization at Rest and During Exercise in Supine and Sitting Position

By

A Granath B Jonsson and T Strandell

The circulatory function in normal young adults has been studied by heart catheterization both at rest and during exercise The reports include both ordinarily trained individuals and athletes (for references see 5 6 17, 37) Elderly subjects however have not previously been studied by this technique but by dye dilution the cardiac output and stroke volume at rest in elderly subjects were found to be lower than in young adults (7)

The present study formed part of a more detailed investigation of the circulatory function in old men (30—35) Besides it was found necessary to collect catheterization data for healthy elderly subjects as the central circulation is nowadays studied for diagnostic reasons in an increasing number of elderly patients Because most routine catheterizations are performed in supine and most studies on exercise physiology in sitting position the subjects were studied in both positions A preliminary report has been issued on the findings concerning the first subjects studied (14)

Submitted for publication February 19 1964

Material

The selection and examination of a material of 27 healthy males aged 61—83 years was discussed in previous papers (30 34) Fifteen of these 27 men volunteered for the present study which also included three other subjects (case nos 26 55 and 69d) described below Four subjects (nos 22 32, 34 and 43) were invited from the Health Survey of the City of Stockholm five from the Labour Exchange (nos 8 25 26 42 and 75) three from old age homes (nos 45 54 and 79) and five from gymnastic groups for the aged (nos 55 56 69b 69c and 70) Case 69d was investigated at the laboratory for scientific reasons before and after an abdominal operation

Different professions were represented such as a porter (case no 8) shipping agent (no 22) watchmaker (no 25) Post Office loading assistent (no 32), merchant (no 34) and judge (no 43) Some subjects were retired but still had contact with their profession such as case no 45 (shipyard worker) no 42 (teacher) and no 56 (official) some were retired and without contact with professional life such as case nos 69b and 70 (metal workers) 69c (asphalter), 75 (engineer) and 79 (carrier)

Case 26 was a worker in the building trade who had been without a job in the last month

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Maximal work								Electrocardiographic findings at exercise test							
								1st test					Repeated tests		
Heart rate (beats/min)	Work load (kpm/min)	Vital capacity (l BTPS)	Residual vol (l BTPS)	FRC/TLC (%)	RV/TLC (%)	FEV%	MVV (l BTPS/min)	Total	ST	VEB	SVEB	QRS	ST	VEB	SVEB
153	810	3.90	2.87	[illegible]	[illegible]	70	154	2	2	1	1	1	3	1	1
168	1 000	4.29	2.48	60	37	67	92	4	1	1	1	4	2	1	2
146	1 150	3.72	2.72	54	37	62	10[illegible]	2	2	1	1	2	2	1	1
170	860	3.31	2.07	51	38	81	118	4	1	4	2	1	2	4	5
1[illegible]4	900	4.[illegible]0	2.60	63	38	66	119	3	1	3	2	1	1	3	5
16[illegible]	8[illegible]0	3.54	2.26	51	39	7[illegible]	117	3	2	1	1	3	2	1	1
16[illegible]	1 000	4.52	1.22	4[illegible]	21	54	99	5	4	4	1	1	4	5	5
183	960	3.64	2.14	8	37	81	10[illegible]	4	4	1	1	2	4	1	5
1[illegible]0	1 100	5.07	2.67	59	34	67	148	4	2	4	1	1	3	5	[illegible]
17[illegible]	[illegible]	2.89	1.90	6[illegible]	40	62	104	3	3	1	1	1	3	1	1
158	900	4.62	2.55	52	36	77	137	5	2	1	5	2	4	1	5
1[illegible]6	660	4.19	3.54	63	46	67	98	4	1	4	3	1	1	5	[illegible]
1[illegible]	7[illegible]0	4.41	2.48	64	36	73	120	5	3	5	2	1	5	5	5
1[illegible]	[illegible]	3.88	3.58	63	48	—	—	1	1	1	1	1	1	1	1
1[illegible]	900	4.69	2.34	59	33	74	[illegible]2	2	2	1	1	1	3	1	5
159	3[illegible]	3.54	[illegible].03	61	36	81	127	5	1	5	2	4	1	5	3
14[illegible]	[illegible]15	3.39	2.00	49	37	70	106	4	4	1	2	4	4	1	2
1[illegible]	8[illegible]1	3.99	2.41	57	37	[illegible]0	117	3.5	2.1	2.3	1.6	1.8	2.6	2.5	3.2
[illegible]	16	0.[illegible]8	[illegible].5	6	6	8	18	1.2	1.1	1.6	1.0	1.2	1.3	1.9	1.8

ed as representative of old men in general. Probably the subjects in this study were more physically fit than the average healthy subject of the same age.

Methods

Before heart catheterization the subjects were thoroughly investigated at the laboratory. The methods employed for electrocardiographic recording, exercise testing, and determination of heart volume, total haemoglobin, blood volume, lung volumes and ventilatory function were described in previous reports on these men (30—34) and the values are given in table I. The findings concerning QRS complexes, ST segments, ventricular ectopic beats (VEB) and supraventricular ectopic beats (SVEB) were independently graded into five classes, class one being normal and class five being regarded as abnormal. The findings at the first exercise test in sitting position and the most marked changes at repeated tests are given in table I.

Right heart catheterization

The technique in this laboratory has been described before (5, 16, 17) and generally only deviations from these descriptions are given below. In 15 cases a double lumen catheter (no. 9) was advanced to the pulmonary artery and in two of these cases another catheter (no. 7, single lumen) was introduced to the right atrium. In two cases only a single lumen catheter no. 7 was used being advanced to the pulmonary artery and wedged position. A polyethylene or teflon catheter was

Table I Some anthropometric data of 17 healthy old men The symbols are explained under Methods

Case no	Age (years)	Height (cm)	Weight (kg)	B S A (m²)	Physical activity		Total Hb (g)	Blood volume (l)	Heart volume (ml)	Heart rate (beats/min)		W_{130} (kpm/min)	
					Earlier	At examin				Standing	Standing supine	Sitting	Supine
8	61	187	87	2 14	2	2	790	5 64	855	67	11	720	800
22	65	178	68	1 87	3	2	760	5 71	530	96	18	650	690
25	65	172	68	1 82	2	2	790	5 34	690	80	10	950	930
26	66	168	69	1 79	3	2	640	4 57	700	61	4	610	700
32	67	170	59	1 70	2	2	635	5 20	585	70	10	670	740
34	67	168	81	1 90	2	2	795	5 85	1,200	78	18	650	670
43	68	179	82	2 02	3	2	820	6 50	980	76	12	680	680
45	69	176	80	1 96	3	2	880	6 98	980	78	16	650	660
42	70	182	73	1 96	2	2	745	5 96	970	70	10	940	870
55	71	178	67	1 86	1	1	640	4 70	745	80	18	450	540
56	71	178	91	2 08	2	2	880	6 29	865	92	24	640	700
69 b	73	172	65	1 78	2	1	650	4 71	640	82	19	480	480
69 c	74	172	75	1 88	3	1	660	5 79	720	100	18	500	640
69 d	74	178	85	2 04	2	1	1,050	6 87	1 000	98	26	310	390
70	75	171	76	1 88	2	2	820	6 12	670	76	12	690	720
75	80	178	58	1 76	2	2	665	5.28	770	86	14	590	580
79	83	163	64	1 68	3	2	600	4 96	670	88	10	480	—
Mean	71	175	73	1 89	2 3	1 8	754	5 68	798	81	15	626	671
S D	6	6	10	0 13	0 6	0 4	118	0 73	179	11	6	161	136

He had been excluded previously because of an arterial pressure of 185/100 mm Hg, but was accepted in this study as he was a border line case (intraarterial pressure 184/87 mm Hg) Case 55 was a retired iron turner who had had pneumonia on three occasions 10—15 years ago His chest X ray was now normal except for slightly flattened sinuses as signs of old adherences He was excluded from the previous studies due to attacks of petit mal starting 10 years ago As a result of Phenemal and Diphydan treatment he was now almost free from attacks (one per month) He was accepted for this study as there was no reason to suppose that his central circulation was influenced by his neurological disease or the medication Case 69d was a retired railway clerk, just admitted to the surgical department for operation of a moderate abdominal hernia which had developed after an operation for prostatic hypertrophy 7 months earlier

The degree of physical activity at examination and earlier in life was graded according to the history in three classes, class one denoting no regular physical training class two a moderate degree of training and class three a high degree of training such as hard bicycling every day cross country running, or hard work e g in the building trade

The mean values of body size and the functional data of these 17 men, obtained in the weeks before the heart catheterization and given in table I, were not significantly different from the mean values of the previously reported larger material of old men (30—34), although the mean heart volume was 90 ml lower Of course the catheterization data in this small sample of old men cannot be regard

Maximal work								Electrocardiographic findings at exercise test							
								1st test					Repeated tests		
Heart rate (beats/min)	Work load (kpm/min)	Vital capacity (l BTPS)	Residual vol (l BTPS)	FRC/TLC (%)	RV/TLC (%)	FEV%	MVV (l BTPS/min)	Total	ST	VEB	SVEB	QRS	ST	VEB	SVEB
153	810	3 90	2 87	55	42	70	154	2	2	1	1	1	3	1	1
168	1 000	4.29	2 48	60	37	62	92	4	1	1	1	4	2	1	2
146	1 150	3 72	2 22	54	37	62	105	2	2	1	1	2	2	1	1
170	860	3 31	2 07	51	38	81	118	4	1	4	2	1	2	4	5
164	900	4.20	2 60	63	38	66	119	3	1	3	2	1	1	3	5
167	850	3 54	2 26	51	39	75	117	3	2	1	1	3	2	1	1
169	1 000	4 52	1 72	46	21	54	99	5	4	4	1	1	4	5	5
183	960	3 64	2 14	58	37	81	105	4	4	1	1	2	4	1	5
160	1 100	5 07	2 67	59	34	67	148	4	2	4	1	1	3	5	2
171	6 0	2,89	1 90	65	40	62	104	3	3	1	1	1	3	1	1
158	900	4 62	2 55	52	36	77	137	5	2	1	5	2	4	1	5
166	660	4 19	3 54	63	46	67	98	4	1	4	3	1	1	3	3
156	750	4 41	2 48	64	36	73	120	5	3	5	2	1	5	5	4
167	670	3.88	3 58	63	48	—	—	1	1	1	1	1	1	1	1
155	900	4 69	2 34	59	33	74	126	2	2	1	1	1	3	1	5
159	735	3 54	2 03	61	36	81	127	5	1	5	2	4	1	5	3
145	615	3 39	2 00	49	37	70	106	4	4	1	2	4	4	1	2
162	851	3 99	2 41	57	37	70	117	3 5	2 1	2 3	1 6	1.8	2 6	2 5	3 2
11	162	0 58	0 57	6	6	8	18	1.2	1 1	1 6	1 0	1 2	1 3	1 9	1 8

ed as representative of old men in general Probably the subjects in this study were more physically fit than the average healthy subject of the same age

Methods

Before heart catheterization the subjects were thoroughly investigated at the laboratory The methods employed for electrocardiographic recording exercise testing and determination of heart volume total haemoglobin blood volume lung volumes and ventilatory function were described in previous reports on these men (30—34) and the values are given in table I The findings concerning QRS complexes ST segments, ventricular ectopic beats (VEB) and supraventricular ectopic beats (SVEB) were independently graded into five classes class one being normal and class five being regarded as abnormal The findings at the first exercise test in sitting position and the most marked changes at repeated tests are given in table I

Right heart catheterization

The technique in this laboratory has been described before (5 16 17) and generally only deviations from these descriptions are given below In 15 cases a double lumen catheter (no 9) was advanced to the pulmonary artery and in two of these cases another catheter (no 7 single lumen) was introduced to the right atrium In two cases only a single lumen catheter no 7 was used being advanced to the pulmonary artery and wedged position A polyethylene or teflon catheter was

introduced into the brachial artery by the percutaneous technique of Seldinger

Pressure recordings were performed with Swema Elema strain gauge manometers (no 456) connected to amplifier units and recorded on an Elema light beam oscillograph ("Mingograf Klinik") In the last four cases (nos 8, 69b, 69c, 75) the pressures were measured with Elema differential transformer transducers (no 490 A) The amplitude response of the recording system (no 456) at varying frequencies was investigated by Holmgren (16) and further checked in the present study With the double lumen catheters the free natural frequency was 10 c/s (no 456) and 20 c/s (no 490 A) and the degree of damping 0 7 and 0 1 respectively Corresponding values with the teflon catheter was 24 c/s and 0 1 (no 490 A) The amplitude response of the recording system should be sufficient for the measurements in the present study (41), but does not allow a detailed analysis of the contours of the curves during exercise The same recording systems were used both in sitting and recumbent position and in the group of earlier studied young men

As reference point for zero pressure in the supine position the mid thoracic level at the insertion of the fourth rib at the sternum was used in contrast to previous reports from this laboratory (5, 6, 17) in which the reference point was the level 5 cm below the insertion of the fourth rib The values in the present study are on an average 4 7 mm Hg higher than if the previous reference level had been used In the sitting position the insertion of the fourth rib at the sternum was regarded as the reference point for zero pressure as in previous studies

Flow studies Cardiac output was measured according to the direct Fick method Expired air was collected for 8—10 minutes at rest supine, and for 5—8 minutes at rest sitting on the bicycle During exercise it was generally collected for 2—3 minutes between the third and sixth minute at each load Blood samples were drawn over one minute from the pulmonary and brachial arteries simultaneously with the collection of expired air During the cardiac output determinations only occasional ectopic beats were recorded and included in the heart rate determination

The pulmonary resistance index was calculated as the difference between the mean pressures in the pulmonary artery and the pulmonary arterial wedge position divided by the cardiac output, the systemic resistance index as the mean pressure in the brachial artery divided by the cardiac output

Blood gas analyses were described in previous reports (5, 17) As there were no differences of probable significance between the haemoglobin concentration of the blood samples from the brachial and pulmonary arteries either at rest or during exercise, the mean value was used for calculation of the oxygen capacity

Mechanical efficiency (ME, %) was calculated as the relation between the mechanical work performed and the increase in energy expenditure during exercise above the predicted basal value (see 5, 31)

Statistical calculations These were done according to Snedecor (29) The following probability (P) levels of significance were used $P < 0.001$*** highly significant, $P < 0.01$** significant and $P < 0.05$* probably significant

Procedure

All the catheterizations but one (case 69 d) were performed ambulatory Most of the subjects had a light morning meal at home (no coffee or tea), but a few preferred to have nothing in accordance with their normal custom They arrived at the hospital at 8 a m , received no sedative or other drugs, and rested supine for at least half an hour About 15 min after the catheters had been introduced, cardiac output and blood pressures were measured at rest in the recumbent position In 7 subjects only recumbent exercise was performed Before the exercise the pressures in the pulmonary artery and the pulmonary arterial wedge position were also measured at rest with the legs on the pedals of the bicycle, the axis of the pedal being located 20—24 cm above the table Two consecutive work loads were used the second generally being twice as high as the first and individually chosen so as to correspond to the heaviest load the subjects could be expected to complete The values of the pulmonary capillary venous (PCV) pressures (21) given below were obtained after 2 minutes exercise at each load In most cases the PCV pressure was also recorded at the end of the first exercise

period before increasing to the second load. The pressures in the brachial artery, pulmonary artery (tip hole) and right ventricle (side hole) were generally recorded both immediately before and after the blood samples were drawn for oxygen saturation, i.e. after approximately 4 and 6 minutes at the loads. The values of these pressures in table II are in most cases mean values from these two occasions.

Nine subjects were also studied in the sitting position. After the measurements at rest supine they were studied after approximately 5 minutes rest sitting on the bicycle ergometer and at two work loads in sitting position. Generally the catheter was fixed to the arm with the tip in the pulmonary artery and no PCV pressure was recorded. After eating one or two sandwiches and some water or milk the subjects rested in supine position for 45—60 minutes. Thereafter they were studied in the recumbent position at rest and at the same two work loads as before. Case 8, however, exercised in sitting position after the supine exercise. He almost fainted at rest sitting and could not complete the second load in sitting position. In case 45 the second sitting work period was interrupted before cardiac output was determined because of frequent ventricular ectopic beats. In case 34 the expired air was not properly collected during sitting exercise and cardiac output could not be determined.

The room temperature ranged between 20 and 24° C and the clothing of the subjects was adjusted according to individual wishes. The venous catheters were flushed by drips of 0.9 % NaCl, of which generally about 1 l was used for a study including sitting exercise. The total blood sampling for the seven cardiac output determinations was 100—120 ml. When sitting exercise was included in the study it was usually finished at about 1 p.m. and the subjects left the laboratory at around 2 p.m. after a light meal.

Complications. In case 25 the catheter slipped down in the right ventricle in the attempt to better position in the pulmonary artery before exercise. Because of series of ventricular ectopic beats during attempts to again advance the catheter to the pulmonary artery the catheterization was interrupted. In case 54, not otherwise described in this study, auricular fibrillation started when the catheter was in the right auricle. He experienced no abnormal sensations but the catheterization was interrupted and sinus rhythm ensued two hours after digitalization. Case 42 was fairly apathetic at the end of the investigation and afterwards became slightly depressed with lack of enterprise and taciturnity lasting for one month. After six months his relatives did not find anything unusual in his personality. He had been very frightened by the thought of catheterization but accepted the invitation to the study without perceptible hesitation. Cases 43 and 45 developed local thrombophlebitic reactions in the arms which did not persist.

Results

The individual data obtained during the heart catheterization will be given in a following paper (15 a). Some mean values are given in table III and V, and in the text mean values $\pm$ S.D. are given unless otherwise stated.

The first work load in the recumbent position was on an average 278 kpm/min (range 200—400) and the second load 550 kpm/min (range 400—800). Corresponding values in sitting position were 278 and 556 kpm/min. The second load in recumbent position corresponded to 84 ± 13 % of the work load at maximal working intensity in that position. Corresponding values in sitting position were 67 ± 9 %. At the heaviest load the mean heart rate was about 130 beats/min and the oxygen uptake 1.5 l/min.

The mean increase of the oxygen capacity of the blood from the brachial and pulmonary arteries during exercise was highly significant. The difference from rest to the second work load amounted to $+1.39 \pm 0.36$ vol % in recumbent and $+0.94 \pm 0.29$ vol % in sitting position, which is in agreement with values observed in young men (5) under similar conditions. In sitting position the oxygen capacity was higher ($P < 0.001$) than

introduced into the brachial artery by the percutaneous technique of Seldinger

Pressure recordings were performed with Swema Elema strain gauge manometers (no 456) connected to amplifier units and recorded on an Elema light beam oscillograph (Mingograf") In the last four cases (nos 8, 69b, 69c, 75) the pressures were measured with Elema differential transformer transducers (no 490 A) The amplitude response of the recording system (no 456) at varying frequencies was investigated by Holmgren (16) and further checked in the present study With the double lumen catheters the free natural frequency was 10 c/s (no 456) and 20 c/s (no 490 A) and the degree of damping 0 7 and 0 1 respectively Corresponding values with the teflon catheter was 24 c/s and 0 1 (no 490 A) The amplitude response of the recording system should be sufficient for the measurements in the present study (41), but does not allow a detailed analysis of the contours of the curves during exercise The same recording systems were used both in sitting and recumbent position and in the group of earlier studied young men

As reference point for zero pressure in the supine position the mid thoracic level at the insertion of the fourth rib at the sternum was used in contrast to previous reports from this laboratory (5, 6, 17) in which the reference point was the level 5 cm below the insertion of the fourth rib The values in the present study are on an average 4 7 mm Hg higher than if the previous reference level had been used In the sitting position the insertion of the fourth rib at the sternum was regarded as the reference point for zero pressure as in previous studies

Flow studies Cardiac output was measured according to the direct Fick method Expired air was collected for 8—10 minutes at rest supine, and for 5—8 minutes at rest sitting on the bicycle During exercise it was generally collected for 2—3 minutes between the third and sixth minute at each load Blood samples were drawn over one minute from the pulmonary and brachial arteries simultaneously with the collection of expired air During the cardiac output determinations only occasional ectopic beats were recorded and included in the heart rate determination

The pulmonary resistance index was calculated as the difference between the mean pressures in the pulmonary artery and the pulmonary arterial wedge position divided by the cardiac output, the *systemic resistance index* as the mean pressure in the brachial artery divided by the cardiac output

Blood gas analyses were described in previous reports (5, 17) As there were no differences of probable significance between the haemoglobin concentration of the blood samples from the brachial and pulmonary arteries either at rest or during exercise, the mean value was used for calculation of the oxygen capacity

Mechanical efficiency (ME, %) was calculated as the relation between the mechanical work performed and the increase in energy expenditure during exercise above the predicted basal value (see 5, 31)

Statistical calculations These were done according to Snedecor (29) The following probability (P) levels of significance were used $P < 0.001$*** highly significant, $P < 0.01$** significant and $P < 0.05$* probably significant

Procedure

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in sitting position Corresponding values at the second work load were 20 7 ± 2 2 % (n = 16) and 19 4 ± 1 6 % (n = 6) This last mean value in recumbent position was not significantly different from previously reported values in sitting position at 600 kpm/min in old men (31), but the mean value in sitting position was slightly lower ($P < 0.05$) Compared with the value at 300 kpm/min (31) there was no difference

Judging from the data given above the same increase of oxygen uptake at rest was observed as in a previous study from this laboratory on young men (5) As in that investigation no significant effect of the catheterization procedure on oxygen uptake during exercise was observed In the present study of old men however, a significant but slight increase of the heart rate during catheterization was found (at the second load + 6 5 % in recumbent and + 4 1 % in sitting position) in contrast to previous findings in young men

Effect of previous exercise on the central circulation at rest

In the 9 subjects who were studied at rest in the recumbent position both before and approximately one hour after the exercise in sitting position the oxygen capacity of the blood was significantly lower (0 58 ± 0 39 ml/100 ml, $P < 0.005$) during the second resting period When the blood loss (60—70 ml) is taken into account this should indicate an increase of the plasma volume of around 4 5 % and of the blood volume of around 2 % assuming an unchanged relationship between the haematocrit of central blood and that of the total blood volume No marked haemodynamic differences were observed between the two determinations at rest (table II) but the stroke volume was slightly lower ($P < 0.05$) on the second occasion, as were the end diastolic pressure in the right ventricle and the PCV pressure When values at rest in the recumbent position are given in tables and figures, those obtained before the sitting exercise are used The effect of previous exercise on the circulation during repeated exercise in recumbent position was not studied here, but in the report of Widimsky et al (39) of four healthy subjects aged 26—52 years the pulmonary artery mean pressure was on an average 3 mm Hg lower during the second work period whereas PCV pressure, cardiac output and stroke volume were unchanged

Arterio-venous oxygen difference, cardiac output and stroke volume

At rest in recumbent position The essential values are given in table III and fig 1,4 The mean cardiac index was 3 06 ± 0 57 l/m²/min and the mean stroke index 45 6 ± 6 0 ml/m² Neither cardiac output nor stroke volume were correlated to heart volume or electrocardiographic findings

The regression of cardiac output on oxygen uptake was highly significant (fig 1), but it should be noted that the cardiac output was calculated from the values of oxygen uptake A part of the correlation between these two parameters should thus be attributed to this fact

Effect of exercise in recumbent position During exercise the cardiac output increased approximately linearly with increasing oxygen uptake (fig 2) There were no individual differences of probable significance between the slope of cardiac output on oygen uptake on transition from rest to exercise and the slope during increasing work loads (+ 1 0 ± 2 1 l blood/min per l oxygen uptake/min)

Table II Effect of previous exercise on circulation data at rest in the recumbent position in 9 healthy men aged 61—83 years Mean individual differences between the second determination at rest one hour after sitting or supine exercise (II) and the first determination at rest (I) are given

			Diff II I	SD of diff	P
Heart rate (beats/min)			3 3	5 4	> 0 1
AV O_2 diff (ml/l)			0 2	4 8	> 0 8
Oxygen uptake (ml/min)			−12	19	> 0 1
Cardiac output (l/min)			−0 31	0 53	> 0 1
Stroke volume (ml)			−7 7	9 9	*
Pressures (mm Hg)	*RV*	S	−1 8	2 9	> 0 05
		De	−1 6	1 33	**
		Di	−0 9	1 54	> 0 1
	PA	S	−1 8	3 0	> 0 1
		D	−1 3	6 7	> 0 5
		M	−1 2	1 9	> 0 05
	PCV	M	−2 1	2.2	*
	BrA	S	1	11	> 0 7
		D	−2	6	> 0 3
		M	1	9	> 0 7
Resistance index (mm Hg/l/min)					
Pulmonary			0 3	0 4	> 0 05
Systemic			1 0	2 1	> 0 1

RV = right ventricle PA = pulmonary artery PCV = pulmonary capillary venous BrA = brachial artery S systolic De = end-diastolic D = initial diastolic D = diastolic M = mean

in supine position, the mean difference at rest being + 1 1 vol % at the first work load + 1 1 vol % and at the second work load + 0 8 vol %

The mean *oxygen saturation* in the pulmonary artery at rest in recumbent position was 73 0 ± 2 7 % In 10 cases the oxygen saturation was also measured in the upper caval vein 1—2 cm above the right auricle before the catheter was placed in the pulmonary artery The oxygen saturation in the pulmonary artery was significantly higher than the saturation in the superior caval vein, the mean individual difference being 2 3 ± 1 9 %

The mean oxygen saturation of the arterial blood was 96 3 ± 1 8 % at rest recumbent and 95 9 ± 1 7 % during the second work load in that position The lowest values recorded were 92 6 % at rest (case 8) and 92 2 % during exercise (case 22) In sitting position the values were at a slightly higher level than in supine position, the mean individual differences amounting to + 2 1 % at rest ($P < 0.05$), + 1 4 % at the first work load ($P < 0.05$) and + 1 4 % at the second load ($P < 0.05$)

Deviation from basal conditions during catheterization

Heart rate The mean individual difference between the heart rate at rest recumbent during the first cardiac output determination and the value recorded at rest under otherwise similar conditions 1—3 weeks before the catheterization was not significant, 0 8 ± 10 0 beats/min At the first and second work loads in recumbent position, however, the heart rates were higher than those previously recorded (obtained by intra or extrapolation as the loads were not always similar), the mean differences being + 7 9 ± 6 8 beats/min (n = 16 $P < 0.001$) and + 8 5 ± 6 8 beats/min (n = 16 $P < 0.001$) respectively In sitting position this difference was 7 0 ± 7 0 beats/min (n = 9 $P < 0.02$) at the first load and + 4 9 ± 5 1 beats/min (n = 7 $P < 0.05$) at the second load

Oxygen uptake The mean uptake at rest in recumbent position was 23 ± 17 % higher than the predicted basal oxygen uptake The mean values for *mechanical efficiency* at the first work load were 17 9 ± 3 7 % *in recumbent and* 16 1 ± 1 8 %

and SD are given and the statistical significance of the differences between sitting (Si) and recumbent (Re)

AV O_2 difference (ml/l)			Cardiac output (l/min)			Stroke volume (ml)		
Rest	Work I	Work II	Rest	Work I	Work II	Rest	Work I	Work II
68 C	111 0	124 3	5 24	9 27	11 61	66.8	90 1	91 7
6.8	7 9	9 8	0 96	1.87	1.68	10 b	11 8	10 0
43.2	89.5	109 1	5 98	10 43	12 93	87 2	99 7	100 0
25 4	21 5	15 2	−0 74	−1 16	−1.32	−20 4	−9 6	−8 3
4 9	6 3	2 4	0 63	1.30	0 55	9 7	10 9	2 3
10	9	7	10	8	6	10	8	6
***	***	***	**	*	**	***	*	***
44 8	93 9	112 1	5 78	10.29	13 08	86 1	98 4	100 8
5 5	9 9	10 1	1 15	1 63	1 66	12.2	11 3	10 [illegible]
17	16	16	17	16	16	17	16	16

The higher values for the arterio-venous oxygen difference at rest both in recumbent and sitting position in the old compared to the young men are evident from table IV as are the lower values for oxygen uptake and cardiac output at rest in recumbent position The regression line of cardiac output on oxygen uptake at rest in the recumbent position representing interindividual variations was on a lower level ($P < 0.001$) in the old than in the young group fig 1) The stroke volumes were also lower in the old except at rest in the sitting position when old and young men had similar values (fig 4) The mean decrease of the stroke volume at rest on transition from recumbent to sitting position was 45 % in the young and 21 in the old

The mean increase of the stroke volume from rest to the second load in sitting position was 81 % in the young and 37 % in the old men The mean increase of the stroke volume from rest to the second load in recumbent position was 6 % in the young and 19 % in the old This last difference however does not seem to be due to age but may be attributable to other differences between the materials In the study of Bevegård et al (4) of 6 non-athletic young volunteers trained for 2—3 weeks prior to the study, the mean increase of the stroke volume from rest to exercise in recumbent position was 28 %

The slopes of cardiac output on oxygen uptake at rest and during exercise were identical in old and young men both in recumbent and sitting position but the level of the lines were lower in the old group ($P < 0.001$) (fig 5) The mean difference in level between the age groups was 2 0 l/min in recumbent and 1 3 l/min in sitting position As the relationships between heart rate and oxygen uptake were the same in the two age groups the differences in cardiac output corresponded to the differences in stroke volume

Intracardiac and intravascular pressures

At rest in recumbent position The most essential values are given in table V The mean pressure in the right auricle was 6 0 ± 1 7 mm Hg (n = 8) The mean values of the pulmonary resistance

Table III The effect of body position on some circulatory data in 10 men aged 61—83 years Mean values position Mean values for the total material of 17 men in recumbent position are given at bottom

	Heart rate (beats/min)			Oxygen uptake (ml STPD/min)		
	Rest	Work I	Work II	Rest	Work I	Work II
Sitting	78 5	101 6	127 7	353	1,024	1,465
SD	8 2	10 1	6 6	48	180	274
Recumbent	68 6	104 2	130 3	255	939	1,437
Difference Si Re	9 9	−2 6	−2 8	98	85	28
SD of difference	7 3	4 8	6 5	37	115	101
No of cases	10	9	7	10	8	6
Probability	**	>0 1	>0 3	***	>0 05	>0 5
Recumbent	67 1	104 2	129 9	255	958	1 464
SD	9 0	7 5	10 1	34	133	215
No of cases	17	16	16	17	16	16

The mean increase of the stroke volume on transition from rest to exercise was highly significant and amounted to 13 6 ± 8 8 ml or 16 % (fig 4) With further increase of the work load the mean increase in stroke volume was insignificant (+ 2 3 ml ± 9 0 P > 0 3), but the individual variations were large

Effect of body position The arterio-venous oxygen difference was significantly higher in sitting than in recumbent position (table III) both at rest (59 %) and during exercise (14 % at the highest load) The stroke volume was significantly lower in sitting position at rest (23 %) and during exercise (8 % at the highest load) (table III)

The cardiac output at rest was significantly lower in sitting compared to recumbent position despite the significantly higher oxygen uptake (table III, fig 1) During exercise in sitting position the increase of the cardiac output in relation to oxygen uptake was the same as the increase during recumbent exercise The regression line for cardiac output on oxygen uptake thus had the same slope in sitting and recumbent position but the line was on a lower level (P < 0 001) in sitting position (fig 3, 5) The mean difference was 1 3 l/min

The stroke volume in sitting position increased on an average by 32 % (P < 0 005) on transition from rest to exercise With further increase of the work load the mean increase in stroke volume (+ 3 3 ± 3 8 ml) was not significant (P > 0 05)

Comparison between old and young men In order to study the effect of age on the central circulation, the data of the old men were compared with previously reported values of young men (5, 17) The latter group comprised 23 young men studied in recumbent position at rest and during exercise In sitting position data from 9 subjects were used, 7 from the study of Bevegård et al (5) and 2 subjects studied later under similar conditions (4) The mean age of these 25 men was 23 3 years (range 16—41) The mean values of height (177 ± 5 cm), weight (69 ± 9 kg) and body surface area (1 87 ± 0 14 m^2) did not differ significantly from the mean values of the old men

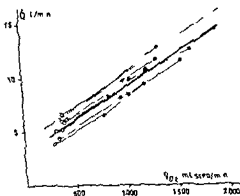


Fig 3 Cardiac output (Q) in relation to oxygen uptake ($\dot{V}_{O_2}$) at rest (open circles) and during exercise (filled circles) in sitting position in 8 men aged 61–83 years. Regression line and 95 % confidence belt for single observations are given. Dotted line represents the regression line in recumbent position (fig 2). Regression equation Q = 0.0070 $\dot{V}_{O_2}$ − 3.01 r = 0.97*** S.D. = ± 0.79 n = 24

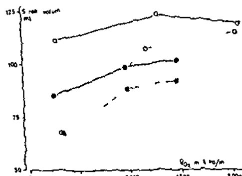


Fig 4 Mean stroke volumes in relation to oxygen uptake ($\dot{V}_{O_2}$) at rest and during exercise in old (filled circles) and young (open circles) men in *recumbent (full lines n = 16 and 23 respectively)* and sitting (broken lines n = 6 and 9 respectively) position

found (r = 0.77*) between the change in pressure from the second to the seventh minute at the first load and the change in PCV pressure (measured after 2 min at the load) from the first to the second work load (0.9 ± 6.5 mm Hg)

The good agreement between the "a" wave and the mean pressure in pulmonary arterial wedge position both at rest and during exercise is illustrated in fig 6. The slope of the height of the "a" wave on the mean PCV pressure was not significantly different from 1.0 (P > 0.05) but the mean value of the "a" wave was 1.5 mm Hg higher than the mean pressure. Variations of the mean PCV pressure may thus be supposed to be a good measure of the variations in filling pressure of the left ventricle in these old men both at rest and during exercise. Under experimental conditions with electrical stimulation of the heart however the relation between the mean left atrial pressure and

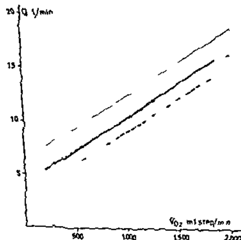


Fig 5 Regression lines for cardiac output (Q) on oxygen uptake ($\dot{V}_{O_2}$) in old (heavy lines) and young men (thin lines) in recumbent (full lines) and sitting (broken lines) position

the left ventricular end-diastolic pressure has been found to change markedly by changes in heart rate and nervous activity (25). The "v" wave corresponded at rest fairly well with the mean pressure, but was significantly higher during exercise (fig 7)

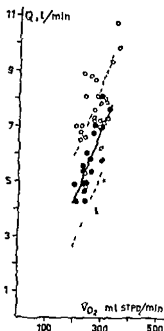


Fig 1 Cardiac output (Q) in relation to oxygen uptake (V_{O_2}) at rest in recumbent (filled circles) and sitting (crosses) position in 17 healthy men aged 61—83 years Open circles denotes values in recumbent position in 25 young men Regression line for old men in recumbent position and 95 % confidence belt for single observations are given $Q = 0\ 0271\ V_{O_2} - 1\ 10$ $r = 0\ 80^{***}$, S D $= \pm 0\ 71$ $n = 17$

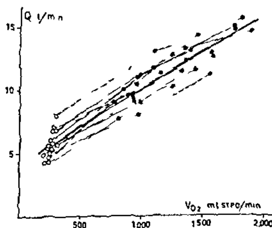


Fig 2 Cardiac output (Q) in relation to oxygen uptake (V_{O_2}) at rest (open circles) and during exercise (filled circles) in recumbent position in 16 old men Regression line and 95 % confidence belt for single observations are given Q $= 0\ 0062\ V_{O_2} + 4\ 11$, $r = 0\ 96^{***}$, S D $= \pm 1\ 01$, $n = 48$

index was 1 19 ± 0 57 and of the systemic resistance index 18 4 ± 4 3 mm Hg/l/min There was no correlation of probable significance between the sagittal diameter of the thoracic cage and any of the pressures at rest, indicating that the chosen reference level for zero pressure did not influence the interindividual variations of the measured pressures

With the feet on the pedals of the bicycle before the supine exercise, and thus with slightly elevated legs, the pressure in pulmonary arterial wedge position increased by 4 1 ± 1 8 mm Hg, ($n = 14$, $P < 0\ 001$) The mean pressure gradient over the peripheral pulmonary vessels did not change (+ 0 3 ± 1 2 mm Hg, $P > 0\ 4$)

Effect of exercise in recumbent position All pressures rose significantly on transition from rest to exercise (table V) except the initial diastolic pressure in the right ventricle ($P > 0\ 3$) At increasing work loads there was no further increase of the pressures of probable significance except for those in the brachial artery, in which the increase in systolic pressure was highly significant and the increases of the mean and diastolic pressures significant

In 9 subjects the mean PCV pressure was also recorded after approximately 7 minutes at the first load, and not only after 2 minutes The mean decrease in pressure from the second to the seventh minute at the first load was 3 8 ± 3 4 mm Hg ($P < 0\ 01$) The simultaneous changes in the pressure drop over the peripheral pulmonary vessels were not significant (+ 0 3 ± 2 5 mm Hg, $P > 0\ 7$) The same response was observed at the second load at which 5 subjects were studied A similar change of the PCV pressure has been reported in patients with mitral stenosis (12) and arterial hypertension (36) A correlation was

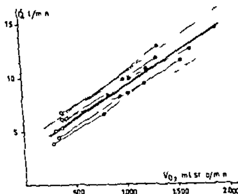


Fig 3 Cardiac output (Q) in relation to oxygen uptake ($\dot{V}_{O_2}$) at rest (open circles) and during exercise (filled circles) in sitting position in 8 men aged 61–83 years Regression line and 95 % confidence belt for single observations are given Dotted line represents the regression line in recumbent position (fig 2) Regression equation Q = 0.0060 $\dot{V}_{O_2}$ + 3.01 r = 0.97*** S D = = ± 0.79 n = 24

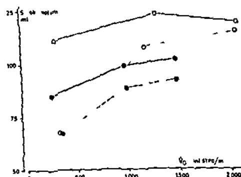


Fig 4 Mean stroke volumes in relation to oxygen uptake ($\dot{V}_{O_2}$) at rest and during exercise in old (filled circles) and young (open circles) men in recumbent (full lines n = 16 and 23 respectively) and sitting (broken lines n = 6 and 9 respectively) position

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The good agreement between the "a" wave and the mean pressure in pulmonary arterial wedge position both at rest and during exercise is illustrated in fig 6 The slope of the height of the "a" wave on the mean PCV pressure was not significantly different from 1.0 (P > 0.05) but the mean value of the "a" wave was 1.5 mm Hg higher than the mean pressure Variations of the mean PCV pressure may thus be supposed to be a good measure of the variations in filling pressure of the left ventricle in these old men, both at rest and during exercise Under experimental conditions with electrical stimulation of the heart however the relation between the mean left atrial pressure and

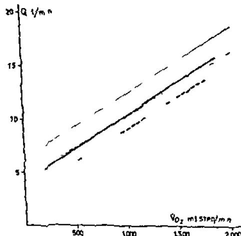


Fig 5 Regression lines for cardiac output (Q) on oxygen uptake ($\dot{V}_{O_2}$) in old (heavy lines) and young men (thin lines) in recumbent (full lines) and sitting (broken lines) position

the left ventricular end-diastolic pressure has been found to change markedly by changes in heart rate and nervous activity (25) The "v" wave corresponded at rest fairly well with the mean pressure, but was significantly higher during exercise (fig 7)

Table IV Comparison between some circulatory data in recumbent (Re) and sitting (Si) positions in a group

	Heart rate (beats/min)				Oxygen uptake (ml/min)	
	Rest		Heaviest work load		Rest	
	Re	Si	Re	Si	Re	Si
Old men	67	79	130	122	255	353
No of cases	17	10	16	6	17	10
Young men	70	84	157	146	285	339
No of cases	23	9	23	9	23	9
Difference	−3	−5	−27	−24	−30	14
Difference in %	−4	−6	−17	−16	−11	4
Probability	>0 3	>0 1	***	***	***	>0 5

The changes of the resistance indices during exercise are shown in fig 8 The mean decrease of the pulmonary resistance index from the value at rest to the heaviest load was 0 16 ± 0 43 mm Hg/l/min ($P > 0\ 1$) and the corresponding decrease of the systemic resistance index 8 3 ± 3 5 mm Hg/l/min ($P < 0\ 001$) The regression lines for systolic and diastolic brachial artery pressures on cardiac output at rest and during exercise are given in fig 9

Effect of body position The mean values of the pressures in sitting position are given in table V At rest only the diastolic pressures of the right ventricle were significantly lower (4—5 mm Hg) in sitting than in recumbent position, but during exercise all the mean values of the pressures in the right ventricle and pulmonary artery were significantly lower (3—8 mm Hg) These lower pressures in sitting position at lower cardiac outputs may be due either to real differences in effective pressures, to the fact that different reference points for zero pressure were used in the different positions, or to differences in the intrathoracic pressures

In the brachial artery significantly higher diastolic and mean pressures were recorded in sitting position at rest (on an average 9—8 mm Hg, n = 9) whereas the higher systolic pressures (on an average 8 mm Hg) were not of probable significance During exercise the pressures were slightly higher (systolic 6—3 mm Hg, diastolic 2—0 mm Hg) in sitting position, but not significantly so As the cardiac output, however, was significantly lower in sitting position, the regression lines of the systolic and mean pressures on cardiac output at rest and during exercise were on a significantly higher level in sitting than in recumbent position, the mean difference in pressure amounting to + 12 5 mm Hg and + 8 5 mm Hg, respectively The slopes were not different in the two positions, nor were there any differences in slope or level for the regression of the diastolic brachial artery pressure on cardiac output The systemic resistance index was thus significantly higher in sitting compared to recumbent position both at rest (+ 22 %) and at the heaviest load (+ 12 %)

Comparison between old and young men The pressures observed in the old men in recumbent position were compared with

of 17 old mean (mean age = 70.5 years) and a group of 25 young men (23 3 years)

Oxygen uptake (ml/min)		AV O_2 diff (ml/l)		Cardiac output (l/min)		Stroke volume (ml)			
Heaviest work load		Rest		Rest		Rest		Heaviest work load	
Re	Si	Re	Si	Re	Si	Re	Si	Re	Si
1 464	1 465	44.8	68.6	5.78	5.24	86	67	101	92
16	6	17	10	17	10	17	10	16	6
2 058	2 078	38.0	60.6	7.65	5.67	111	67	118	114
23	9	23	9	23	9	23	9	23	9
−594	−563	6.8	8.0	−1.87	−0.43	−25	0	−17	−22
−29	−27	18	13	−24	−8	−23	0	−14	−19
***	***	***	*	***	>0.3	***	>0.9	**	*

previously reported data on 23 young men (5 17) recalculated to the same reference point for zero pressure as in the present study (fig 9 and 10)

At rest the mean pressure in pulmonary arterial wedge position was slightly lower in the old men (−2 6 mm Hg P <0 01) as was the mean value of the diastolic pressure in the pulmonary artery (−2 2 mm Hg P 0 01) The mean systolic pressure in the brachial artery was higher in the old men (+25 mm Hg P < 0 001)

During exercise the heaviest load in recumbent position was lower in the old than in the young men (1 46 l O_2/min compared to 2 06 l O_2 min) as was the cardiac output (13 1 l min compared to 18 5 l min) At the heaviest load the systolic and mean pressures in the brachial artery were higher (P 0 001) in the old men (+32 and +19 mm Hg respectively) as were the end-diastolic pressures in the right ventricle (+7 0 mm Hg) the systolic (+10 3 mm Hg) diastolic (6 2 mm Hg) and mean pressure in the pulmonary artery (+9 0 mm Hg) (fig 10) The initial diastolic pressures of the right ventricle were significantly higher in the group of old men (+5 3 mm Hg) and the pulmonary arterial wedge pressures probably significantly higher (+6 5 mm Hg) (fig 10) When the individual mean values of the pressures at the two work loads were used and the subjects with only one recording during exercise were included, the mean values for the pulmonary arterial wedge pressures did not change but the difference was found to be significant (P < 0 005 10 young and 16 old men) The slightly higher mean value recorded for right ventricular systolic pressure (+5 3 mm Hg) in the old men was not significantly higher (P > 0 1)

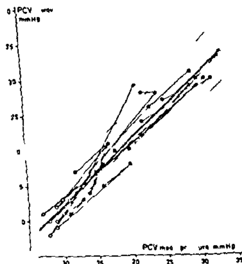
The resistance indices of the pulmonary and systemic circulation were higher in the group of old men both at rest and during exercise (fig 8) The slope of the regression line of the pressure gradient over the peripheral pulmonary vessels on cardiac output was not significantly different in the two age groups (P > 0 05), but the level of the line was higher in the old men (P < 0 001) If the old man with the highest pressure gradient (case 55) was excluded the slope of the regression line was higher in the old men (P <

Table V. Pressures, mm Hg, at rest and during exercise in 17 men aged 61—83 years. Mean values ± standard deviation. No. of cases in brackets. a = "a" wave, v = "v" wave

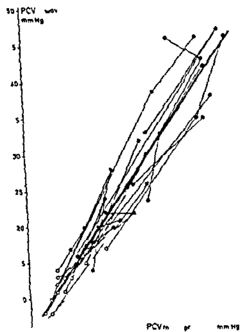
		Recumbent position			Sitting position		
		Rest	Work I	Work II	Rest	Work I	Work II
BrA	S	149.2±16.3 (17)	179.9±17.7 (15)	195.3±17.6 (15)	150.3±12.0 (9)	176.8±14.5 (8)	193.5±20.4 (8)
	D	75.1± 9.4 (17)	82.9±11.8 (15)	86.0±11.9 (15)	78.4±10.2 (9)	77.4± 9.2 (8)	82.0±11.7 (8)
	M	102.5±10.5 (17)	122.8±14.5 (15)	129.7±15.5 (15)	106.1±10.7 (9)	122.8±15.4 (9)	126.5±17.2 (8)
PCV	M	9.9± 2.3 (16)	22.0± 5.9 (16)	22.1± 8.1 (14)	5.0± 2.8 (2)		
	a	11.8± 2.4 (16)	23.3± 5.4 (16)	22.5± 7.7 (13)			
	v	12.1± 2.5 (16)	30.1± 8.4 (16)	29.2±12.6 (13)			
PA	S	24.3± 2.8 (17)	45.3± 8.1 (16)	45.7± 8.6 (16)	21.1± 4.0 (10)	36.6± 6.6 (9)	39.1± 7.6 (8)
	D	10.1± 2.7 (17)	19.9± 4.9 (16)	21.3± 5.8 (16)	8.2± 4.2 (10)	13.3± 6.6 (9)	13.9± 5.7 (8)
	M	15.9± 2.6 (17)	31.6± 6.8 (16)	32.4± 7.4 (16)	12.9± 4.2 (10)	22.1± 6.8 (9)	25.4± 8.1 (9)
RV	S	25.8± 3.2 (17)	48.1± 8.2 (14)	51.4± 8.4 (14)	22.5± 4.3 (10)	38.6± 6.4 (9)	45.2± 9.7 (9)
	De	8.1± 2.0 (17)	13.5± 3.9 (14)	13.1± 5.6 (14)	3.2± 4.3 (10)	7.0± 5.2 (9)	7.8± 5.7 (9)
	Di	3.4± 2.0 (17)	4.3± 4.0 (14)	2.9± 3.9 (13)	−0.5± 4.5 (10)	−0.6± 3.6 (9)	−0.4± 3.5 (9)

0.05), as was the level ($P < 0.001$). The slope of the mean pressure in the brachial artery on cardiac output was higher in the group of old men ($P < 0.001$). The slope of the regression line of the systolic pressure in the brachial artery on cardiac output was also higher in the old men ($P < 0.01$) (fig. 9). The slope of the diastolic pressure on cardiac output was similar in both age groups ($P > 0.1$) but the level was significantly higher in the old men (fig. 9).

In sitting position at the heaviest work load some of the pressures were significantly higher in the old than in the young men. This was valid for the average systolic (+ 39 mm Hg) and mean pressures in the brachial artery (+ 17 mm Hg), the systolic pressure in the pulmonary artery (+ 12 mm Hg) and the end diastolic pressure in the right ventricle (+ 7.5 mm Hg). The mean pressure in the pulmonary artery was also higher in the old men (+ 8 mm Hg, $P < 0.05$).



F g 6 PCV a wa e n rela on to PCV mean pres u e n r cumben pos on at res (open c es an l du ng exerc se (f ll d c es n 16 old men Hea y fu l n d no es the regress on l ne lo d l nes he 95 conf dence bel fo single observa ons B oken l ne d no s he 45 l ne PCV a 0 93 PCV m an + 2 78 r 0 96*** SD 2 0 n 4



F g 7 PCV wa e n rela on o PCV mean pressu e Symbols as in f g 6 r 0 95*** n 45

Discussion

The c rc latory funct on in young l ealth y nd d als l as earl er been stud ied at tl ese laborator es by tl e same meth ods and proced res as in th s report (5 6 17 Therefore tl e effect of aging on tl e c c lat on m gl t be evaluated by a compari on of these mater als subject to all tl e reservat ons tl at must be made for transversal st l es

Ca d a ou put

In accordance w tl otl er invest ga t ons 22 tl e mean card ac o tput at rest n s p ne pos t on was found to be l wer in l l tl an n young ind vid als Only l alf of tl s decl ne corresponded to tl e decrea e in oxygen uptake ith i crea ng age Tl erefore the card ac out put as related to the oxygen uptake was s gn f cantly lower n old than in young persons Th s d fferen e corresponded to an average total arterio-venous oxygen d fference of 44 8 ml l n old and 38 0 ml l n young persons The decrease of tl e card ac output ith age may be pro- port onal througl out tl e body or more marked in some organs and even absent in others The last v ew is supported l y earl er f nd ngs of markedly reduced renal blood flow in old age (— 53 % from the 4th to the 9th decade)(11) and a fairly uncl anged calf blood flo v (2) As tl e renal c rc lat on has a very lo v arterio- venous oxygen d fference in comparison v th other organs the marked decrea e of the renal flow may at least partly ex pla n tl e h gher arterio-veno s oxygen d fference in old age

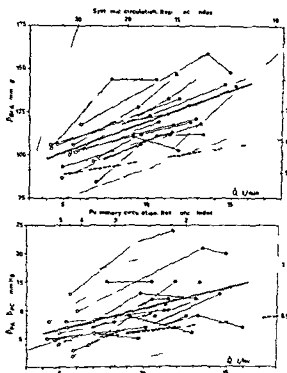


Fig. 8. Mean pressure ($\bar{P}$) in brachial artery (above) and pressure drop over peripheral pulmonary vessels in relation to cardiac output ($\dot{Q}$) in recumbent position in 16 old men. Symbols as in table II. The oblique lines are *isoresistance index* lines. Regression lines (heavy lines) ± 95 % confidence belts for single observations. Broken heavy lines denote regression lines in 23 normal young men (from ref. 5, 17). Regression equations: $\bar{P}_{BrA} = 3.61\ \dot{Q} + 83.4$, r = 0.69***, S.D. = ± 13.0, n = 46. $(\bar{P}_{PA} - \bar{P}_{PCV}) = 0.34\ \dot{Q} + 2.8$, r = 0.48**, S.D. = ± 3.3, n = 36.

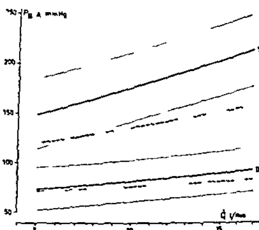


Fig. 9. Systolic (S) and diastolic (D) pressures in the brachial artery in relation to cardiac output ($\dot{Q}$) at rest and during exercise in recumbent position in 16 old men. Regression lines (heavy lines) ± 95 % confidence belts for single observations (thin lines). Broken lines denote regression lines in 23 young men. S = 5.59 $\dot{Q}$ + 121, r = 0.75***, S.D. = ± 17.1, n = 46. D = 1.70 $\dot{Q}$ + 65.0, r = 0.49***, S.D. = ± 10.4, n = 46.

The increase of the cardiac output during exercise is almost exclusively restricted to the skeletal muscles in young persons, although the regional distribution to other organs is also changed (see 37). The findings of the same mean increases of cardiac output with increasing oxygen uptake in old and young men should then suggest that also the increase of the blood flow to the working muscles is the same. Similar (9) or only slightly higher values (Strandell, to be published) of the arterio-venous oxygen difference of femoral venous blood during exercise have also been found in old compared to young men.

Stroke volume

The mean heart rate at a given oxygen uptake was the same in old and young men both at rest and during exercise. The lower mean cardiac output at a given oxygen uptake in the old men was therefore a result of a lower mean stroke volume corresponding to a higher arterio-venous oxygen difference.

In normal young subjects interindividual variations in stroke volume during exercise are related to corresponding variations in heart volume, total haemoglobin and circulatory function during exercise measured as working intensity at heart rate 170 (W_{170}) (17). In the presently studied group of old men the mean stroke volume during exercise was less strongly correlated to these parameters (fig. 11 a—c), the correlation coefficients

being 0 56*, 0 46 and 0 56* respectively (n = 16) The higher values for W_{170} in relation to stroke volume in the old men corresponds to the higher mean arterio venous oxygen difference during exercise

The old men with heart volumes above 800 ml had lower stroke volumes in relation to heart volume compared to the regression line of young subjects (fig 11a) (− 27 ml ± 16, mean ± S D, n = 7) than the old men with smaller heart volumes (− 8 ± 12 ml, n = 9) This difference (P < 0 02) was not related to any differences in electrocardiographic findings The question may arise whether or not the more marked deviation from the regression line in the old men with large heart volumes was connected with high degree of physical training earlier in life For it was observed in a group of old former racing cyclists (18) that most of their increase in heart volume was persistent despite their not more than normal physical working capacity at the time of the investigation The result of the present classification of the physical activity earlier in life does not support this hypothesis but the classification was rather crude The decrease of stroke volume in relation to heart volume with rising age was discussed in a previous report 32)

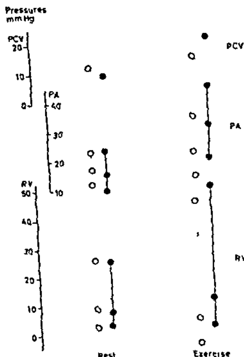


Fig 10 Mean values for pressures at rest and at the heaviest work load in recumbent position in 17 old (filled circles) and 23 young men (open circles) Symbols as in table II and V

Pressures

Marked structural changes occur with increasing age in the arterial vessels accompanied by functional changes with a successive increase of the stiffness of the aorta and its main branches (see 38) Thereby the function of the aorta as an arterial compression chamber decreases with age but this is at least partly compensated by the increase of the aortic volume 28 39) However in the normal pressure ranges the increase in aortic volume for a given increase in pressure has been found to be lower in old age, and still more so when arteriosclerotic changes are marked (28), so the compensation of the increased rigidity with age is not complete Also the heart wall seems to develop increased stiffness in old age which has been attributed to a more rigid intercellular collagenous connective tissue (19)

The effect on the left ventricular performance of ejection into outflow systems with various elastic properties has been studied in anaesthetized dogs (27) It was observed that ejection into a rigid outflow system the same mean aortic pressure as a distensible system, was

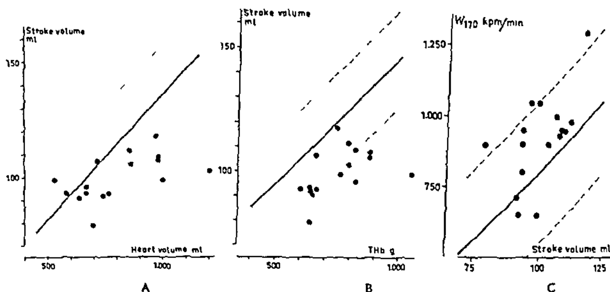


Fig 11 Mean stroke volume during exercise in relation to A) heart volume B) total haemoglobin (THb) and C) working intensity at heart rate 170 (W_{170}) in 16 old men Regression lines ±2 S D for normal young subjects are given (ref 5 7)

followed by elevation of both the left ventricular peak systolic pressure and the left ventricular end diastolic pressure When the elevation of the arterial reservoir was adjusted so as to keep the left ventricular peak systolic pressure constant, ejection into the rigid outflow system was still associated with increased left ventricular end diastolic pressures, even though stroke work was reduced These findings are quite in accordance with those of Wiggers (10) and others and indicate that when the concentration pattern of the ventricles is changed by secondary factors, e g by changes in input or output loads, the initial tension and the amplitude of contraction alter in the same direction according to Starling s law of the heart They also suggest that a rigid outflow system causes an increased outflow load above that predicted from peak systolic pressures and stroke volume

In the present study there was an increase with age of the systemic vascular resistance index at rest as in a previous report (23) During exercise involving increase of the diastolic pressure the pulse pressure increased more in the old than in the young men, which is in accordance with previous observations (1, 20) and would be expected as a result of the decreased function of the aorta as an arterial compression chamber in old age In view of these observations and the previous discussion an increase also of the end diastolic pressures in the left ventricle might be expected At rest, however, the mean PCV pressure was slightly lower in the old men, but during exercise both the PCV pressure and the end diastolic pressure in the right ventricle were higher, as were the systolic pressures in the brachial and pulmonary arteries

When the right ventricular end diastolic pressure was markedly increased during exercise in the present study, the configuration of the pressure curve generally showed an early-diastolic dip (fig 12) and thus resembled the pressure curves described in constrictive pericarditis (13)

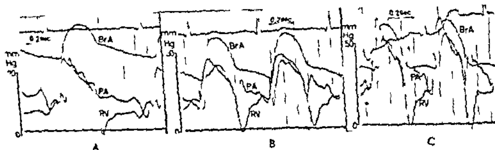


Fig 12 The most marked early-diastolic dip during exercise (case 70) A – at rest heart rate 81 beats/min stroke volume 71 ml B – at 300 kpm/min heart rate 104 beats/min stroke volume 88 ml C – at 600 kpm/min heart rate 125 beats/min stroke volume 103 ml Symbols as in table II

Similar curves have been described in other conditions with increased rigidity of the heart wall such as endocardial fibrosis (10) and myocardial fibrosis (26) The observation of a more rigid collagenous connective tissue in old than in young human hearts (19) may partly explain the high filling pressures during exercise in these old men together with increased systolic pressure loads

In isolated left ventricles of dog hearts the mechanical impedance of the ventricle was calculated as the ratio of intraventricular pressure to inflow (8) It was observed that increases both in aortic pressure and in heart rate were accompanied by increased mid filling impedance and a shortened time for filling when impedance was lowest The changes in stroke output during these experimental conditions appeared to be closely related to changes in the ease and duration of filling In the presently studied old men the increased brachial artery pressures compared to young men may be expected to have caused an increase of the diastolic impedance to which the decrease of stroke volume with rising age might be related

The high filling pressures of the heart during exercise in the athletes studied by Bevegård et al (6) were interpreted as a condition in which, in normal hearts, high filling pressures are needed for maintaining extremely high stroke volumes in the short time available during exercise

The increased filling pressures of the heart and the lower stroke volumes in the old men may thus have other explanations than primary myocardial factors affecting the contractility Both the mean stroke volume and the mean pressures in the brachial and pulmonary arteries increased on transition from rest to exercise simultaneously with the increase in filling pressures Thus the calculated stroke work for the right and left ventricles increased and no descending limb of the ventricular function curves was observed This corresponds to the normal ventricular function curve in normal dog hearts (3) and contrasts to the "descending limb" observed after e g coronary artery constriction (3) In the present study the end-diastolic pressure in the right ventricle and the PCV pressure during exercise were not correlated to heart volume or degree of ST depression in the exercise electrocardiogram Nor were negative correlations observed between the stroke work of the ventricles and the heart volume or degree of electrocardio-

graphic abnormalities, as in patients with arterial hypertension (36) It should also be noted that in rigid hearts the energy losses connected with internal friction should be higher than in more distensible hearts

Acute digitalization with 1 6 mg lanatoside C in 6 of the presently reported old men was not followed by a significant increase of stroke volume or cardiac output, nor by a decrease of the PCV pressure or end-diastolic pressure in the right ventricle (15)

Although the present findings in old men may be explained by secondary factors affecting the contraction pattern of the ventricles, they suggest an increased load and a decreased volume-forwarding function of the heart Attention has recently been called by Meerson (24) to some similarities between the changes in the relative compensatory phase of experimental aortic stenosis in animals and senile myocardial changes In both conditions he observed hypertrophy of myocardial fibres, myocardial fibrosis and similarities concerning biochemical changes

Summary

1 Right heart catheterization was performed in 17 healthy men aged 61—83 years, including estimation of cardiovascular pressures and cardiac output at rest and during different intensities of exercise in recumbent and sitting positions The data were compared with corresponding values of previously studied young men (5, 17)

2 The old men had lower stroke volumes and cardiac outputs at rest in the recumbent position than the group of young men, but similar values in sitting position During exercise the increase in cardiac output was the same in old and young men The regression line of cardiac output in relation to oxygen uptake at rest and during exercise was thus on a lower level in the old men, both in recumbent (—2 l/min) and sitting (—1 3 l/min) *position, indicating a higher* arteriovenous oxygen difference

3 The increase in stroke volume from rest to the second work load was 19 % in the recumbent and 37 % in the sitting position The stroke volumes during exercise were lower in the old than in the young men in both positions

4 The systolic pressures in the brachial artery were higher in the old men both at rest and still more during exercise The regression of the diastolic pressure on cardiac output was on a slight but significantly higher level in the old men

5 At rest in the recumbent position the mean PCV pressure was slightly but significantly lower in the old men At the heaviest work load, on the contrary, the pressures in the group of old men were significantly higher in the pulmonary *arterial wedge position, in the pulmonary* artery and in the right ventricle in diastole, the most marked cases showing an early-diastolic dip There was no correlation of probable significance between the filling pressures during exercise and the heart volume at rest or the degree of ST depression in the exercise electrocardiogram At rest and during exercise the height of the "a" wave corresponded to the mean pressure in the pulmonary arterial wedge position

6 The resistance indices of *the pulmonary* and systemic circulations were higher in the old men, both at rest and *during* exercise

7 The increase in *filling pressures* from rest to exercise in the old men oc

curred simultaneously with an increase of the stroke volume The significance of the different circulatory findings in the old compared to the young men are discussed

Acknowledgement

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7 The increase in filling pressures from rest to exercise in the old men oc-

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The Department of Clinical Physiology Karolinska sjukhuset Stockholm, Sweden

Relationships Between Cardiac Output, Stroke Volume and Intracardiac Pressures at Rest and During Exercise in Supine Position and Some Anthropometric Data in Healthy Old Men

By

A Granath and T Strandell

In a previous paper (9) the pressures and flows obtained during right heart catheterization of 17 healthy males aged 61—83 years were reported Compared to previously studied groups of young men (2 12) both cardiac output and stroke volume were lower in the old men both at rest and during exercise in the supine position The filling pressures of the heart, measured as the mean pressure in pulmonary arterial wedge position, and the right ventricular end-diastolic pressure respectively were slightly lower in the group of old men at rest During exercise however they were significantly higher in the old men despite lower work load and cardiac output

The present study formed part of a more detailed investigation of the circulatory function in old men (17—22) and is a direct sequel to the previous paper (9) The aim of the present investigation was to study the relationships between pressure and flow during catheterization in supine position and some measurements of circulatory, pulmonary and metabolic function as well as body size and age

Material

The selection and examination of the presently studied 17 *healthy men* aged 61—83 years was discussed in the previous paper (9) as was the technique of the right heart catheterization

Statistical calculations

These were made according to Snedecor (16) The following probability levels of significance were used $P < 0.001$*** *highly* significant, $P < 0.01$** significant and $P < 0.05$* probably significant. Multiple regression analyses were performed by the method of least squares

The following variables were used in the study in which all regression and total correlation coefficients were first computed

Total arteriovenous oxygen difference (ml/l) cardiac output (Q l/min) at rest and slope and level of the regression line for cardiac

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The Department of Clinical Physiology, Karolinska sjukhuset, Stockholm Sweden

Relationships Between Cardiac Output, Stroke Volume and Intracardiac Pressures at Rest and During Exercise in Supine Position and Some Anthropometric Data in Healthy Old Men

By

A Granath and T Strandell

In a previous paper (9) the pressures and flows obtained during right heart catheterization of 17 healthy males aged 61—83 years were reported Compared to previously studied groups of young men (2 12) both cardiac output and stroke volume were lower in the old men, both at rest and during exercise in the supine position The filling pressures of the heart, measured as the mean pressure in pulmonary arterial wedge position and the right ventricular end-diastolic pressure respectively were slightly lower in the group of old men at rest During exercise however, they were significantly higher in the old men, despite lower work load and cardiac output

The present study formed part of a more detailed investigation of the circulatory function in old men (17—22) and is a direct sequel to the previous paper (9) The aim of the present investigation was to study the relationships between pressure and flow during catheterization in supine position and some measurements of circulatory, pulmonary and metabolic function as well as body size and age

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Material

The selection and examination of the presently studied 17 healthy men aged 61—83 years was discussed in the previous paper (9) as was the technique of the right heart catheterization

Statistical calculations

These were made according to Snedecor (16) The following probability levels of significance were used $P < 0.001$*** highly significant $P < 0.01$** significant and $P < 0.05$* probably significant Multiple regression analyses were performed by the method of least squares

The following variables were used in the study in which all regression and total correlation coefficients were first computed

Total arterio-venous oxygen difference (ml/l) cardiac output (Q l/min) at rest and slope and level of the regression line for cardiac

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The following variables were used in the study in which all regression and total correlation coefficients were first computed

Total arterio-venous oxygen difference (ml l), cardiac output (Q l/min) at rest and slope and level of the regression line for cardiac

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output on oxygen uptake The slope and level were computed from the individual values at rest and at the two work loads By the method of least squares the slope of the individual regression line (l blood per min /l oxygen uptake per min) was identical to the slope between the values at rest and at the second load The level of the line (l/min) was defined as the individual mean value of cardiac outputs and oxygen uptakes at rest and during exercise in relation to the regression line of the total material A subject with positive level thus had a higher mean cardiac output in relation to oxygen uptake than the average of the group

Pulmonary resistance index (RI) and systemic RI at rest (9) as well as slope (mm Hg/l/min) and level (mm Hg) of the pressure drop over the peripheral pulmonary vessels on cardiac output at rest and during exercise were also used, as were slope and level of systolic and mean brachial artery pressure on cardiac output

Stroke volume (ml), pulmonary capillary venous (PCV) mean pressure, right ventricular (RV) systolic (S) and end diastolic (De) pressure, pulse pressure in the pulmonary artery (PS_{S-D}) and in the brachial artery (BA_{S-D}) heart rate (beats/min), oxygen uptake ($\dot{V}_{O_2}$ ml/min), ventilation in relation to oxygen uptake ($V_E/\dot{V}_{O_2}$, l_{BTPS}/l_{STPD}) and respiratory variations of the pulmonary artery systolic pressure (Respir var PAs mm Hg) were used as variables including the values at rest (R), at the second work load (II) the change from rest to the first load (I—R) and the change from the first to the second load (II—I) For stroke volume PCV pressure and RV_{De} pressure the mean values of work load I and II (W) were also used All pressures were measured in mm Hg The total ventilation at rest (V_E l_{BTPS} min) the oxygen pulse at rest ($\dot{V}_{O_2}$ divided by heart rate) and the increase of the oxygen uptake at rest above the predicted basal value (according to Harris and Benedict) were also included as variables The increase of the heart rate from the second to the sixth minute at the first and second loads were used as well as the intra- or extrapolated value of the 2—6 minute heart rate increase at heart rate 130 beats/min ($St\ st_{130}$) as estimates of the heart rate steady state during exercise

The following variables obtained from studies of the subjects prior to heart catheterization were also used Age (years), body weight (kg), height (cm), body surface area (BSA m²) calculated according to Du Bois height weight formula and used as an index of body size, total heamoglobin (g), haemoglobin concentration, blood volume (l), heart volume in prone position (ml), working intensity at heart rate 130 (W_{130}, kpm/min), heart rate (HR_{max}) and work load (W_{max} kpm/min) at maximal working intensity and the logarithm of the lactate concentration of arterialized finger blood sampled during sitting exercise at heart rate 130 (Log $lact_{130}$ log mE/l) In a part of this study the logarithm of the lactate concentration at 600 kpm/min (Log $lact_{600}$) was also used as a variable

The total lung capacity (TLC), vital capacity (VC), residual volume (RV), the quotients RV/TLC (%) and FRC/TLC (%), as well as forced expiratory volume in one second ($FEV_{1.0}$), $FEV_{1.0}$ expressed as percentage of VC (FEV%) and maximal voluntary ventilation (MVV) at a free breathing rate, were used as measures of lung volumes (l, BTPS) and ventilatory function

The electrocardiographic findings concerning the QRS complexes, ST segments, ventricular ectopic beats (VEB) and supraventricular ectopic beats (SVEB) at rest and during the exercise tests were denoted ECG_{QRS} ECG_{ST}, ECG_{VEB} and ECG_{SVEB} respectively They were independently graded into five classes, class one being normal and class five being regarded as abnormal (17) The findings at the first exercise test in sitting position including the total assessment of the ECG based on the most marked abnormality recorded were used as ECG variables as well as the most marked changes at repeated tests (repeated)

The degree of physical activity at examination and earlier in *life* (*earlier*) was graded according to the history in three classes class one denoting no regular physical training and class three a high degree of training

The individual data recorded before heart catheterization were mainly given in table I of the previous paper (9) Some supplementary data are given in table I of this paper The methods used for obtaining these data were described in detail in previous papers (17—21)

Table I Data obtained during right heart catheterization in 17 healthy men aged 61—83 years

Case no (Age)	Position	Work load kpm/min	Heart rate beats/min	Oxygen uptake (ml STPD/min)	VE	O₂ capacity (ml/100 ml)	O₂ sat (%)		AV O₂ diff (ml/l)	Cardiac output (l/min)	Stroke volume (ml)	Pressures mm Hg													Resistance in Ū	
							BrA	PA				RA	RV			PA			PCA			BrA			Pulmonary circ (mm Hg/l/min)	Systemic circ (mm Hg/l/min)
													S	De	Di	S	D	M	M	a	v	S	D	M		
8	Re	Rest	13	2 0		20.5	97.6	74.4	38.4	7.03	112	5	23	7	4	24	10	15	9	9	13	157	83	99	0.85	14.1
	Re	250	90	809	19	1.2	95.7	33.7	90.0	9.16	107	5	34	9	0	32	13	22	20	18	22	161	77	112	0.52	11.6
(75)	Re	500	108	1312	22	21.[illegible]	96.3	48.1	106.3	17.53	116	2	35	7	0	31	12	21	16	15	22	175	84	119	0.72	9.5
	Re	Rest	64	[illegible]		20.2	93.2	72.4	43.0	6.23	97	4	22	6	0	22	8	14	8			151	74	108	0.96	17.3
	Si	Rest	77	427		21.5	100.4	68.9	67.6	6.14	80	−3	17	0	−4	18	7	11	3			155	83	111	1.30	18.1
	Si	250	90	932	17	20.3	93.4	49.1	117.6	8.10	90	−5	24	−2	−3	24	8	14	4			161	70	112	1.36	13.8
	Si	500	98									−1	26	1	−1	27	8	16				175	77	112		
22	Re	Rest	79	295		19.4	94.9	75.6	42.6	6.92	88		28	7	3	24	8	15	7			127	59	84	1.16	12.1
	Si	Rest	79	393		20.3	95.5	63.8	66.1	5.95	75		31	6	3	27	10	16				147	77	97		16.3
(21 5)	Si	300	103	1019	17	20.7	93.5	42.8	106.5	9.84	95		43	10	2	36	13	21				189	73	115	—	11.7
	Si	600	130	1621	20	21.0	93.4	30.0	132.2	12.96	94		54	6	1	42	13	25				204	81	125		10.2
	Re	Rest	79	275		19.0	94.5	74.9	38.3	7.18	91	4	26	7	3	26	10	16	9	11	8	148	66	102	0.97	11.2
	Re	300	103	909	20	19.7	94.9	48.4	[illegible]	9.78	94		42	13	4	40	17	28	15	17	20	179	67	108	1.33	11.0
	Re	600	127	1,541	22	20.3	92.2	35.2	117.0	13.17	101		60	16	4	47	22	30	18	20	21	207	74	118	0.91	9.0
25 (71 5)	Re	Rest	72	318		20.1	98.1	78.3	41.7	7.63	106		22	9	3	23	8	14				133	73	98		12.8
[illegible]	Re	Rest	63	242		19.4	96.8	68.7	56.6	4.28	68		26	7	5	25	9	17	11	13	13	184	97	124	1.87	29.0
	Re	250	103	800	20	19.9	100.4	49.7	102.9	7.77	75		50	15	6	50	22	34	24	28	33	204	93	144	1.93	18.5
(24 5)	Re	500	178	1227	23	20.3	97.6	40.9	117.3	10.46	82		49	15	8	47	23	34	22	28	23	215	96	144	1.43	13.8
3[illegible]	Re	Rest	[illegible]	239		19.0	97.8	73.5	48.3	4.95	77	1	27	7	1	22	8	14	9	10	14	139	67	93	1.21	18.8
	Re	350	94	959	22	20.2	98.5	42.0	117.1	8.19	87		36	8	0	33	12	20	13	13	20				0.98	
(21)	Re	600	117	1526	[illegible]	19.4	98.9	34.8	133.2	11.46	98		37	4	0	32	11	19	11	11	17	186	72	113	0.87	9.9
34	Re	Rest	57	207		18.2	[illegible]	69.2	48.7	4.25	75		30	14	10	29	18	22	16	17	17	152	81	106	1.18	21.9
	Si	Rest	67	285		19.8	96.6	61.6	71.2	4.00	60		25	9	7	24	16	20				[illegible]	93	122		30.5
(75)	Si	300	97			20.3	97.0	43.7	110.2				40	12	6	45	27	35				187	94	133		
	Si	600	135			21.0	96.3	42.0	115.9				49	11	6	51	24	41				221	106	100		

	Re	Rest	62	213		16.8	95.5	67.6	47.9	4.44	78	6	24	11	8	25	14	19	13	15	15	150	79	108	1.13	24.3
	Re	300	103	834	23	18.5	91.9	51.0	82.3	10.13	98		50	16	9	49	27	38	29	29	35	181	87	123	0.69	12.1
	Re	600	135	1,439	24	19.7	95.9	46.5	98.9	14.55	108		55	15	7	60	31	45	33	33	46	204	95	141	0.89	9.7
43	Re	Rest	57	236		19.2	98.1	72.8	50.7	4.65	82	9	25	5	3	25	11	18	13	15	15	155	80	106	1.08	22.8
	Re	350	107	1,076	20	20.0	97.6	53.3	90.6	11.88	111					42	21	28	21	29	32	188	100	133	0.89	11.2
(26)	Re	700	142	1,711	23	20.8	95.3	12.0	112.1	15.26	107					45	29	29								
45	Re	Rest	87	296		18.1	97.2	78.0	36.9	8.02	92	8	28	8	3	25	11	17	10	13	13	158	91	119	0.62	14.8
	Si	Rest	97	374		19.0	98.3	65.3	64.8	6.08	63		23	8	3	25	12	17								
(25)	Si	400	126	1,331	17	19.4	96.6	13.9	104.5	12.74	101		39	11	1	42	17	28				155				12.2
	Si	800											11	14	1			33								
	Re	Rest	100	282		17.0	96.8	70.4	36.6	7.71	77		23	4	1	19	7	12	6	7	7	148	80	105	0.65	13.6
	Re	400	122	1 082	22	18.1	94.2	49.6	81.7	13.24	109		41	10	2	43	21	32	22	22	30	180	89	124	0.68	9.4
	Re	800	149	1 773	22	20.0	95.7	40.7	111.1	15.96	107		50	15	3	50	24	36	30	30	42	208	99	146	0.44	9.1
42	Re	Rest	60	245		17.6	93.3	70.7	40.6	6.03	101	6	34	8	3	30	12	19	9	12	12	169	81	118	1.66	19.6
(23.5)	Re	300	112	1 324	13	18.6	99.8	48.0	98.2	13.48	120	11	66	16	11	66	27	48	32	30	47	228	104	159	1.56	11.8
	Re	600	130	1,855	18	19.5	97.0	34.3	124.3	14.92	115	6	47	8		46	26	37	22	24	33	225	95	148	1.34	9.9
55	Re	Rest	65	231		19.3	93.8	72.9	41.3	5.59	86	5	22	8	3	24	12	17	9	12	12	176	85	106	2.33	19.0
(20)	Re	250	98	910	17	20.5	96.6	50.5	96.5	9.43	96		53	12	6	48	20	32	17	21	20	183	88	128	2.33	13.6
	Re	500	134	1,293	22	21.0	95.6	43.5	110.7	11.68	87		46	9	5	46	22	33	12	17	16	205	105	147	2.05	12.6
56	Re	Rest	65	259		18.1	96.7	73.3	44.5	5.82	90	6	24	9	3	20	9	13	9	12	12	144	77	103	0.52	17.7
	Si	Rest	81	372		19.2	100.7	65.1	70.3	5.29	65		27	7	3	26	12	17				157	90	120		22.7
(23)	Si	350	100	1,215	17	19.8	98.7	41.4	115.4	10.53	105		43	12	1	44	17	26				185	87	127		12.1
	Si	700	137	1 890	20	20.2	98.6	34.3	131.6	14.36	105		52	16	0	45	19	30				200	91	134		9.3
	Re	Rest	73	223		17.5	93.5	69.7	42.6	5.23	72		22	9	3	20	8	13	7	8	8	138	73	97	1.15	18.5
	Re	350	105	1,059	21	18.3	98.8	45.7	99.5	10.64	101		53	21	6	48	21	33	23	26	38	170	82	119	0.85	11.2
	Re	700	137	1,721	23	19.5	98.2	41.0	113.4	15.18	111		62	22	3	54	25	41	29	31	46	201	91	140	0.92	9.2
69b	Re	Rest	57	231		19.0	98.0	74.3	46.9	4.93	86		25	6	1	24	8	14	10	11	11	129	60	87	0.81	17.6
	Si	Rest	77	294		19.7	98.4	62.5	72.7	3.91	51		18	1	−2	18	4	10	7			125	60	89	0.77	22.8
(22)	Si	200	95	789	16	20.7	97.9	41.1	119.8	6.59	69		44	4	−1	32	5	15				156	66	103		15.6
	Si	400	125	1,187	19	20.8	96.6	36.5	127.2	9.33	75		56	6	−1	31	8	17				173	70	112		12.0
	Re	Rest	61	247		18.5	97.1	72.9	46.7	5.29	87		25	5	0	21	7	12	7	10	10	125	52	81	0.95	15.9
	Re	200	107	933	13	19.5	94.1	49.2	88.4	10.55	99		50	9	0	40	13	26	16	18	24	167	74	111	1.14	10.5
	Re	400	140	1 302	17	20.3	94.6	39.6	112.8	11.54	82		61	7	−2	31	14	24	14	14	14	176	77	117	1.04	10.1
69c	Re	Rest	73	268		16.4	96.0	73.0	39.7	6.75	92		24	7	2	22	6	13	8	8	10	133	67	96	0.9	14.2
	Si	Rest	80	375		17.8	95.8	64.7	[illegible]	[illegible]	83		21	−1	−4	21	[illegible]	11				154	78	108		[illegible]
(22.5)	Si	200	101	984	12	18.2	[illegible]	41.9	[illegible]	[illegible]	[illegible]		33	1	−6	33	8	18				171	74	111		11.8
	Si	400	120	1 320	17	[illegible]	[illegible]	32.9	113.0	[illegible]	97		[illegible]	0	−7	[illegible]	[illegible]	21				[illegible]	71	[illegible]		9.1

Table 1 (cont.)

Case no. Th d	Test	Work load kpm/min	Heart rate beats/min	Oxygen uptake ml STPD/min	ME	O2 capacity ml/100 ml	O2 sat % BrA	O2 sat % PA	AV O2 diff (ml/l)	Cardiac output (l/min)	Stroke volume (ml)	Pressures mm Hg RA	RV S	RV De	RV Di	PA S	PA D	PA M	PCV M	PCV a	PCV v	BrA S	BrA D	BrA M	Resistance index Pulmonary circ. (mm Hg/l/min)	Resistance index Systemic circ. (mm Hg/l/min)
(2 5)	Re	Rest	0	2(		16 3	93 9	70 6	47 1	5 13	80		2	5	2	27	6	13	3			151	72	102	1 78	18 1
	Re	00	103	9(4	13	17 0	96 ?	47 4	81 9	11 35	110		46	10	1	41	15	29	17	21	28	173	73	112	0 97	9 9
	Re	400	1 9	1 304	17	17	91	38 5	107 5	13 33	104		68	10	0	41	15	29	14	14	18	176	76	112	1 13	9 4
9l	Re	Rest	74	2?		21 4	96 7	74 6	49 1	5 34	72		26	8	4	24	12	16	8	10	8	143	79	100	1 50	18 7
(24)	Re	200	112	9 0	11	22 3	94 4	56 9	81 7	11 22	100					43	22	32	22	22	26	188	95	133	0 89	11 9
	Re	400	133	1 9	19	22 9	96 4	55 9	94.8	12 96	37					38	19	28				203	100	145		11 2
0	Re	Rest	81	307		18 2	93 1	70 2	57 6	5 74	71	5	22	11	3	19	8	12	9	10	11	140	70	102	0 35	17 8
(25)	Si	Rest	78	342		19 2	100 0	60 1	78 7	4 35	56		23	4	−3	18	7	11				152	78	107		24 6
	Si	300	100	1 030	17	0 0	98 5	38 6	121 7	8 46	85		41	10	−4	36	11	18				169	75	116		13 7
	Si	600	1 C	1 557	21	20 0	98 2	31 0	136 3	11 42	91		0	12	−3	35	15	21				188	80	122		10 7
	Re	Rest	77	2 7		17 7	94 9	70 0	45 1	5 70	74		25	10	4	21	9	12	6	7	6	110	71	99	0 88	17 1
	Re	300	104	974	20	18 5	98 2	49 9	100 5	9 19	88		46	18	0	43	18	28	20	20	26	164	76	112	0 98	12 2
	Re	600	175	1 557	2?	19 3	94 3	32 3	120 5	12 88	103		56	19	−3	52	23	34	30	29	35	179	78	121	0 47	9 4
75	Re	Rest	64	298		16 7	98 0	73 2	49 3	5 39	84		29	8	3	27	11	18	13	15	15	149	71	102	1 30	18 9
	Si	Rest	81	375		17 4	99 1	50 7	75 7	4 95	61		21	−4	−8	16	3	8				145	77	102		20 6
(18 5)	Re	200	101	972	13	17 3	97 7	37 2	106 5	9 13	90		55	16	4	53	22	37	30	29	43	161	71	111	0 99	12 2
	Re	500	124	1 409	19	17 9	94 7	28 7	119 0	11 84	95		57	18	5	52	20	36	25	27	46	165	68	103	1 27	8 7
79	Re	Rest	60	193		16 0	94 9	70 3	40 3	4 91	82		24	9	3	26	11	17	8	10	10	152	66	99	2 04	20 2
	Si	Rest	68	307		16.8	93 4	63 2	61 1	5 02	74		19	2	0	18	6	8				148	69	99		19 7
(21)	Si	200	107	899	14	17 3	98 3	40.5	101 8	8 24	80		40	5	−1	37	14	24				196	80	130		15 8
	Si	400	121	1 212	18	18 0	98.2	38 5	111 0	10 63	88		43	4	0	43	15	25				218	80	138		13 0
	Re	Rest	66	193		15 7	95 6	68 8	45 5	4 18	63	4	20	7	3	21	8	16	8	10	10	150	69	98	2 39	23 4
	Re	200	100	67	16	16 4	97 8	45 4	85 0	9 02	93		51	16	11	50	27	38	31	30	38	171	68	113	0 67	12 5
	Re	400	120	1 110	20	17 0	96 6	38 8	99 0	11 52	96		56	19	10	56	25	43	34			204	80	131	0 78	11 4

Th d = sagittal thoracic diameter Re = recumbent S = sitting Me = mechanical efficiency BrA = brachial artery PA = pulmonary artery RA = right auricle RV = right ventricle PCV = pulmonary capillary venous S = systolic De = end-diastolic Di = initial diastolic D = diastolic M = mean a = a wave v = v wave

Table II Some data obtained before (lactate values) or during heart catheterization in 17 healthy men aged 61—83 years The symbols are explained under Methods

Case no	Log $lact_{600}$	Log $lact_{130}$	Heart rate steady state (beats/min)			$\dot{V}_E$ (l BTPS/min)			$\dot{V}_E/\dot{V}_O$ (l BTPS/l STPD)			Respir var PA_5 (mm Hg)		
			I	II	130	R	I	II	R	I	II	R	I	II
8	0 49	0 67	2	6	10	10 1	25 9	27 5	37 3	29 8	28 2	6	10	16
22	0 15	0 19	1	3	3	13 0	25 0	45 0	44 2	27 5	29 2	7	10	20
25	0 20	0 50	—	—	—	12 1	—	—	37 9	—	—	—	—	—
26	0 59	0 59	0	6	7	8 0	23 2	35 3	32 9	29 0	28 8	6	8	11
32	0 52	0 59	4	8	10	7 3	25 0	37 9	30 6	26 0	24 8	2	3	8
34	0 42	0 48	3	4	4	6 6	21 7	41 9	31 8	26 0	29 1	3	6	6
43	0 40	0 63	2	12	9	8 2	28 7	47 3	34 7	26 7	27 7	4	9	15
45	0 33	0 41	4	8	5	11 9	26 8	45 6	40 2	24 7	25 7	5	9	12
42	0 15	0 58	7	7	7	6 2	39 7	59 1	25 4	30 0	31 8	4	6	11
55	0 85	0 61	1	14	11	7 3	22 3	36 4	31 0	24 5	28 1	2	6	15
56	0 56	0 60	6	14	11	10 0	30 7	64 4	38 6	29 0	37 4	6	6	12
69b	0 81	0 75	11	15	13	7 6	26 5	40 9	33 0	28 4	31 4	3	5	11
69c	0 70	0.53	2	6	8	7 1	21 4	30 3	26 5	22 2	22 2	3	6	8
69d	—	—	5	9	9	8 1	24 2	33 5	30 8	25 5	27 3	5	8	9
70	0 43	0 57	1	1	1	10 1	23 1	44 4	33 3	25 0	28 6	4	6	8
75	0 37	0 37	2	1	1	8 3	27 7	42 2	36 5	28 5	30 0	0	8	9
79	0 67	0 50	5	8	10	6 9	23 5	41 2	34 7	30 7	36 2	2	9	9
Mean	0 48	0 52	3 5	7 6	7 4	8 7	26 0	42 1	34 1	27 1	29 2	3 9	7.2	11 3
SD	0 22	0 13	2 8	4 4	3 7	2 1	4 5	9 5	4 8	2 4	3 8	1 9	2 0	3 7

Results

The individual catheterization data are given in table I, some supplementary data are given in table II

Most of the relationship are summarized in tables III—XVI The variables, physical activity and ECG, were given according to graded scales and were known not to be normally distributed Therefore they were only used as independent variables and in tables III—XVI the significance of the regression coefficients were given instead of correlation coefficients The symbols used in the text and the tables are explained under Methods and in table III It should be noted that some of the relationships given in these tables and in the text are partly explained by the fact that the same measurement was included as a component of both the dependent and the independent variable This is especially the case for interrelationships between arterio-venous oxygen difference, cardiac output, stroke volume, oxygen uptake and slope and level of cardiac output on oxygen uptake Still, however, it might be of interest to study which of the variables in the Fick equation (oxygen uptake = heart rate × stroke volume × arterio venous oxygen difference) are most closely related to each other Mean values ± SD are given in the text unless otherwise stated

Arterio-venous oxygen difference

The mean arterio venous oxygen difference at rest was 44 8 ± 5 5 ml/l (n = 17)

Table III Correlation (r) and regression coefficients (b) between cardiac output at rest (dependent variable y) and some anthropometric data (independent variables, x) in 17 healthy men aged 61—83 years For symbols see Methods

Independent variable	r	b
Systemic RI R	−0.85***	−0.22
Oxygen uptake R	0.80***	0.077
Stroke volume R	0.73***	0.068
Vent lat on R	0.72**	0.40
AVO₂ diff R	−0.71**	−0.15
Heart rate R	0.70**	0.088
Level of Q on $\dot{V}_{O_2}$[1]	0.65**	0.84
Slope of Q on $\dot{V}_{O_2}$	−0.57*	−0.61
Stroke volume W[1]	0.53*	0.058
$\dot{V}_{O_2}$ R % of pred.	0.57*	0.034
PCV pressure R	−0.50*	−0.23

R = at rest I = at the first work load II = at the second work load W = mean of I and II

[1] n [illegible]

Table IV Slope of cardiac output on oxygen uptake at rest and during exercise (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
$\dot{V}_{O_2}$ R % of pred	0.66**	0.043
Stroke volume I R	0.65**	0.073
Heart volume	0.[illegible]7**	0.0034
PCV pressure II	0.58*	0.064
Cardiac output R	0.57*	0.5?
Respir var PAs II − I	−0.57*	0.1?

n 14

It was negatively related to stroke volume at rest (r = −0.78***, b = 0.35), cardiac output at rest (r = −0.71**, b = [illegible]3.4), to the level of cardiac output on oxygen uptake at rest and during exercise (r = 0.60*, b = 4.0) and to the mean stroke volume during exercise (r = 0.52*, b = 0.30). It was not correlated to oxygen uptake at rest (r

Table V Level of cardiac output on oxygen uptake at rest and during exercise (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
Stroke volume W	0.69**	0.059
Blood volume	0.67**	0.74
Cardiac output R	0.65**	0.50
Weight	0.60*	0.050
AVO₂ diff R	−0.60*	−0.089
ECG ST	[1]P<0.025	0.41
Heart volume	0.54*	0.0075
Total haemoglobin	0.53*	0.0037

[1] Significance of b

Table VI Stroke volume at rest (y) in relation to some anthropometric data (x) in 17 old men Symbols as in table III and under Methods

Independent variable	r	b
AVO₂ diff R	−0.78***	−1.73
Cardiac output R	0.73***	7.7
Stroke volume W[1]	0.70**	0.81
Stroke volume II[1]	0.57*	0.61
Height	0.57*	1.16
Oxygen pulse R	0.56*	21.8
W_{130}	0.53*	0.040

[1] n = 16

— 0.16), heart rate at rest (— 0.21), oxygen pulse at rest (0.07), increase of oxygen uptake at rest above the predicted basal value (— 0.14) or age (0.07)

Cardiac output

At rest The mean cardiac output was 5.78 ± 1.15 l/min (n = 17) Some of the relationships (P < 0.05) with other data are given in table III An increase of the heart rate by 10 beats/min above the mean value was accompanied by a mean increase of the cardiac output of 0.91/min An increase of the oxygen uptake at rest of 23 % above the predicted basal value,

which was the average increase in this study, was accompanied by a mean increase of the cardiac output of 0 8 l/min Therefore the quite "basal" mean cardiac output in this group of old men should be expected to be around 5 0 l/min The cardiac output was not found to be related to body surface area (r = 0 31) or age (— 0 28) The correlation coefficient with the pulse pressure in the brachial artery at rest was — 0 48 (b = — 0 05, P < 0 1)

The mean individual value for the *slope of cardiac output on oxygen uptake* at rest and during exercise was 6 16 ± 0 99 l blood per min /l oxygen uptake per min n = 16) This slope was steeper the more "basal" the oxygen uptake at rest, the larger the heart volume and the higher the PVC pressure at the second load (table IV) When heart volume (b/εb**) and cardiac output at rest (**) were combined as independent variables, the residual standard deviation decreased to ± 0 61 l blood per min /l oxygen uptake per min

The mean individual *level of cardiac output on oxygen uptake* at rest and during exercise in relation to the regression line for the group was 0 03 ± 0 84 l/min (n — 16) This level was higher the larger the stroke volume during exercise, the larger the blood volume, weight and heart volume, and the lower the arterio-venous oxygen difference at rest (table V) There was no correlation with age (r = — 0 04) or W_{130} (r = — 0 07)

Stroke volume (fig 1)

At rest the mean stroke volume was 86 1 ± 12 2 ml (n = 17) It was better related to arterio-venous oxygen difference than to oxygen pulse (table VI) It was not related to heart rate or oxygen uptake at rest, nor to age (r = — 0 35),

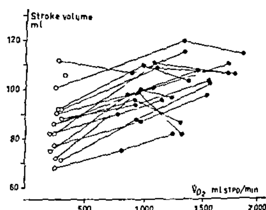


Fig 1 Stroke volume in relation to oxygen uptake ($\dot{V}_{O_2}$) at rest (○) and during exercise (●) in 17 healthy men aged 61—83 years

body surface area (0 36), weight (0 16) or heart volume (0 01) When height (*) and W_{130} (*) were combined as independent variables, the residual standard deviation decreased to ± 9 2 ml

At the second work load the mean stroke volume was 100 8 ± 10 5 ml (n = 16) It was significantly and positively related to blood volume (y = 9 48x + 46 8, SD = ± 8 0 ml) and body surface area, less so to weight, W_{130}, W_{max}, vital capacity and MVV (table VII) The correlation coefficients with heart volume and age were 0 48 (P < 0 1) and — 0 32, respectively The regression of stroke volume on physical activity and ECG_{ST} (repeated) was positive but not of probable significance (P < 0 1) HR_{max} (b = — 0 46) was of probable significance as independent variable in combination with blood volume When blood volume (b — 11 2***) and MVV (b = 0 25**) were combined as independent variables (n = 15) the residual standard deviation decreased to ± 5 2 ml or ± 5 2 % of the mean value

The mean stroke volume during exercise was 99 9 ± 9 9 ml (n = 16) The relationships with body surface area (y = 52 3x + 0 8 SD = ± 7 2 ml) and some

Table VII Stroke volume at the second work load (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
Blood volume	0.68**	9.48
PSA	0.60**	52.2
Weight	0.62*	0.6[illegible]
W_{130}	0.62*	0.046
W_{max}	0.58*	0.042
Stroke volume R	0.57*	0.52
Vital capacity	0.55*	9.8
Max vol vent[1]	0.53*	0.32
Level of Q on $\dot{V}O_2$	0.52*	6.[illegible]

n = 15

Table VIII Mean stroke volume during exercise (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
BSA	0.71**	52.3
Stroke volume R	0.70**	0.60
Level of $\dot{Q}$ on $\dot{V}O_2$	0.69**	8.2
Blood volume	0.69**	8.9
Weight	0.61*	0.60
Height	0.61*	0.99
Vital capacity	0.57*	9.5
Heart volume	0.56	0.030
Cardiac output R	0.53*	4.9
A-V O_2 diff R	0.52*	0.9[illegible]
$W_{[illegible]}$	0.51*	0.030
[illegible] repeated	P 0.0[illegible]	3.8

Significance of b

other data are given in table VIII. When blood volume (b = 8.2**) and the arteriovenous oxygen difference *at rest* (b = 0.79*) were combined as independent variables (n = 16) the residual standard deviation decreased to ± 6.2 ml or 6.2 % of the mean value

The mean *increase of the stroke volume from rest to the first work load* was 13.5 ± 8.8 ml ($P < 0.001$, n = 16). This increase was only related to the individual slope of cardiac output on oxygen uptake (r = 0.65**), to the blood volume (0.59*) and to the heart volume (0.57*). It was not related to the values of blood volume per kg body weight (r = 0.25) or heart volume per kg body weight (0.44).

The difference between the stroke volume at the second and the first work load (II—I) was + 2.3 ± 9.0 ml ($P > 0.3$, n = 16). This difference was positively related to the anamnestic degree of physical activity (b = 15**) and to the difference in pulmonary artery pulse pressure between the second and the first load (PA_{s-D} II—I) (r = 0.60*, b = 0.84), it was negatively related to the heart rate increase from the second to the sixth minute at the second load (St st II r = −0.62*, b = −1.3) and to the heart rate at the second load (r = −0.53*, b = −0.47). The correlation coefficients with BA_{s-D} II—I PVC II—I and RV_{D} II were 0.51, 0.48 and 0.48 respectively ($P < 0.1$). Combining the degree of physical activity (b = 12**) with PA_{s-D} II—I (b = 0.60 $P < 0.02$) as independent variables the residual standard deviation decreased to ± 5.2 ml. With physical activity and heart rate at the second load or physical activity and St st II the corresponding values were ± 5.6 and ± 5.7 ml respectively.

If it had been assumed that the whole difference between the stroke volume at the two work loads was due to methodological errors the coefficient of variation for a single determination would have been ± 6.4 %. But taking the physiological relationships into account (mainly the degree of physical activity), the remaining variance corresponded to an error of ± 3.7 % for a single determination of stroke volume during exercise

which was the average increase in this study, was accompanied by a mean increase of the cardiac output of 0 8 l/min Therefore the quite "basal" mean cardiac output in this group of old men should be expected to be around 5 0 l/min The cardiac output was not found to be related to body surface area (r = 0 31) or age (— 0 28) The correlation coefficient with the pulse pressure in the brachial artery at rest was — 0 48 (b = — 0 05, P < 0 1)

The mean individual value for the *slope of cardiac output on oxygen uptake* at rest and during exercise was 6 16 ± 0 99 l blood per min /l oxygen uptake per min n = 16) This slope was steeper the more "basal" the oxygen uptake at rest, the larger the heart volume and the higher the PVC pressure at the second load (table IV) When heart volume (b/εb**) and cardiac output at rest (**) were combined as independent variables, the residual standard deviation decreased to ± 0 61 l blood per min /l oxygen uptake per min

The mean individual *level of cardiac output on oxygen uptake* at rest and during exercise in relation to the regression line for the group was 0 03 ± 0 84 l/min (n = 16) This level was higher the larger the stroke volume during exercise, the larger the blood volume, weight and heart volume, and the lower the arterio venous oxygen difference at rest (table V) There was no correlation with age (r = — 0 04) or W_{130} (r = — 0 07)

Stroke volume (fig 1)

At rest the mean stroke volume was 86 1 ± 12 2 ml (n = 17) It was better related to arterio-venous oxygen difference than to oxygen pulse (table VI) It was not related to heart rate or oxygen uptake at rest, nor to age (r = — 0 35), body surface area (0 36), weight (0 16) or heart volume (0 01) When height (*) and W_{130} (*) were combined as independent variables, the residual standard deviation decreased to ± 9 2 ml

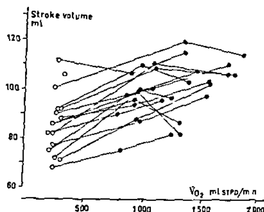


Fig 1 Stroke volume in relation to oxygen uptake ($\dot{V}_{O_2}$) at rest (○) and during exercise (●) in 17 healthy men aged 61—83 years

At the second work load the mean stroke volume was 100 8 ± 10 5 ml (n = 16) It was significantly and positively related to blood volume (y = 9 48x + 46 8, SD = ± 8 0 ml) and body surface area, less so to weight, W_{130}, W_{max}, vital capacity and MVV (table VII) The correlation coefficients with heart volume and age were 0 48 (P < 0 1) and — 0 32, respectively The regression of stroke volume on physical activity and ECG_{ST} (repeated) was positive but not of probable significance (P < 0 1) HR_{max} (b = — 0 46) was of probable significance as independent variable in combination with blood volume When blood volume (b = 11 2***) and MVV (b = 0 25**) were combined as independent variables (n = 15), the residual standard deviation decreased to ± 5 2 ml or ± 5 2 % of the mean value

The mean stroke volume during exercise was 99 9 ± 9 9 ml (n = 16) The relationships with body surface area (y = 52 3x + 0 8, S D = ± 7 2 ml) and some

Table VII S roke volume at the se ond wo k load (y) in rela on to some anthropometric data (x) n 16 old men Symbols as in table III and under M hod

Independent ariable	r	b
Plood olume	0.68**	9.48
PSA	0.6 **	57.2
We gh	0.6 *	0.f
?? se	0.6?*	0.046
W_m	0.59*	0.01
S oke lume R	0.57*	0.52
V al apa y	0.55*	9.8
Max ol en	0.53*	0.32
Level of Q on V_{O_2}	0.5 *	f.5

n 15

Table VIII M an stroke volume during exe e (y) n la on to some anth opometric data (x) n 16 old m n S mbol a in table III and unde M thod

In ependen a ab	r	b
BSA	0.71**	5? 3
S roke olum R	0.70**	0.60
Lev l of Q on V_{O_2}	0.69**	8.2
B oo l ume	0.68**	8.9
W gh	0.61*	0.60
H gt	0.61*	0.99
V al ap y	0 7*	9.5
H art o ume	0.56*	0.030
C rd ou pu R	0 3*	4?
A V O diff R	0.57*	0.9
W_s	0.51*	0.0 6
I X r epea ed	P 0.05	3.8

S gn an of b

Ier l tx are g en n table VIII W] en Hood ol me b 8 2** and tl e arte-r s e o voxygen l fference at rest b 9* ere coml ned as i depend en var ables n If tl e res dual a la l dev at on decrea ed to 6 ? ml or 6 ? % of tl e mean value

Tl e mean i rea e of the stroke volume f om *rest to the first work load* was 13 5 ± 8 8 ml ($P < 0.001$ n — 16) Th s increase was only related to the individual slope of card ac outp t on oxygen uptake (r — 0 65**) to the blood volume (0 59*) and to tl e heart volume (0 57*) It was not related to the values of blood volume per kg body weight (r — 0 25) or heart volume per kg body we ght (0 44)

The d fference between the stroke volume at the se ond and the first work load (II—I) was + 2 3 ± 9 0 ml ($P > 0.3$ n = 16) Th s d fference was pos t vely related to the anamnest c degree of physical activity (b — 15**) and to tl e difference in pul monary artery pulse pressure between the second and the first load (PA_{S-D} II—I) (r — 0 60* b = 0 84) it was negatively related to the heart rate increase from the second to the sixth minute at the second load (St st II r — —0 62* b — —1 3) and to tl e heart rate at the second load (r — —0 53* b = —0 47) Tl e correla t on coeffic ents with BA_{S-D} II—I PVC II—I and RV_{De} II were 0 51 0 48 and 0 48 respectively ($P < 0.1$) Comb n ng tl e degree of pl ysical act vity (b — 12**) v itl PA_{S-D} II—I (b — 0 60 $P < 0.02$) as in lependent variables tl e res dual standard deviat on decreased to ± 5 2 ml With pl ys cal act v ty and heart rate at tl e second load or phys cal act vity and St st II tl e corresponding values were ± 5 6 and ± 5 7 ml respectively

If it l ad been assumed that the whole d fference bet een tl e stroke volume at tl e t o work loads was due to methodo logical errors tl e coeff c ent of variation f r a s ngle determ nat on would l ave been + 6 4 % But taking tl e pl ys olog ical relationsl ps into account (ma nly the degree of pl ys cal act vity) tl e remain ing variance corresponded to an error of — 3 7 % for a s ngle determ nat on of stroke volume d ir ng exercise

which was the average increase in this study, was accompanied by a mean increase of the cardiac output of 0 8 l/min Therefore the quite "basal" mean cardiac output in this group of old men should be expected to be around 5 0 l/min The cardiac output was not found to be related to body surface area (r = 0 31) or age (— 0 28) The correlation coefficient with the pulse pressure in the brachial artery at rest was — 0 48 (b = — 0 05, P < 0 1)

The mean individual value for the *slope of cardiac output on oxygen uptake* at rest and during exercise was 6 16 ± 0 99 l blood per min /l oxygen uptake per min n = 16) This slope was steeper the more "basal" the oxygen uptake at rest, the larger the heart volume and the higher the PVC pressure at the second load (table IV) When heart volume (b/εb**) and cardiac output at rest (**) were combined as independent variables, the residual standard deviation decreased to ± 0 61 l blood per min /l oxygen uptake per min

The mean individual *level of cardiac output on oxygen uptake* at rest and during exercise in relation to the regression line for the group was 0 03 ± 0 84 l/min (n = 16) This level was higher the larger the stroke volume during exercise, the larger the blood volume, weight and the lower the arterio-heart volume, and the lower the arterio-venous oxygen difference at rest (table V) There was no correlation with age (r = — 0 04) or W_{130} (r = — 0 07)

Stroke volume (fig 1)

At rest the mean stroke volume was 86 1 ± 12 2 ml (n = 17) It was better related to arterio-venous oxygen difference than to oxygen pulse (table VI) It was not related to heart rate or oxygen uptake at rest, nor to age (r = — 0 35),

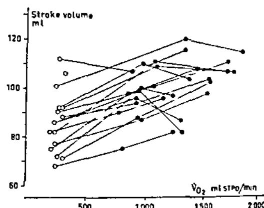


Fig 1 Stroke volume in relation to oxygen uptake ($\dot{V}_{O_2}$) at rest (○) and during exercise (●) in 17 healthy men aged 61—83 years

body surface area (0 36), weight (0 16) or heart volume (0 01) When height (*) and W_{130} (*) were combined as independent variables, the residual standard deviation decreased to ± 9 2 ml

At the second work load the mean stroke volume was 100 8 ± 10 5 ml (n = 16) It was significantly and positively related to blood volume (y = 9 48x + 46 8, SD = ± 8 0 ml) and body surface area, less so to weight, W_{130}, W_{max}, vital capacity and MVV (table VII) The correlation coefficients with heart volume and age were 0 48 (P < 0 1) and — 0 32, respectively The regression of stroke volume on physical activity and ECG_{ST} (repeated) was positive but not of probable significance (P < 0 1) HR_{max} (b = — 0 46) was of probable significance as independent variable in combination with blood volume When blood volume (b = 11 2***) and MVV (b = 0 25**) were combined as independent variables (n = 15), the residual standard deviation decreased to ± 5 2 ml or ± 5 2 % of the mean value

The mean stroke volume during exercise was 99 9 ± 9 9 ml (n = 16) The relationships with body surface area (y = 52 3x + 0 8, S D = ± 7 2 ml) and some

Table VII Stroke volume at the second work load (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
Blood volume	0 68**	9 48
BSA	0 66**	57 2
Weight	0 62*	0.65
W_{130}	0 62*	0 036
W_{max}	0.59*	0 047
Stroke volume R	0 57*	0 53
Vital capacity	0 55*	9.8
Max vol vent	0.53*	0.32
Level of Q on V_{O_2}	0 51*	[illegible]

n 15

Table VIII Mean stroke volume during exercise (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
BSA	0 71**	52 3
Stroke volume R	0 70**	0 60
Level of Q on V_{O_2}	0 19**	8.2
Blood volume	0 68**	8 9
Weight	0 61*	0 60
Height	0 61*	0.99
Vital capacity	0 57*	9 5
Heart volume	0 56*	0 030
Cardiac output R	0 53*	4.3
A V O_2 diff R	0 52*	−0 97
W_{130}	0 51*	0 036
ECG, repeated	P 0 05	3.8

Significance of b

other data are given in table VIII When blood volume (b = 8 2**) and the arteriovenous oxygen difference at rest (b = − 11 7**) were combined as independent variables (n = 16) the residual standard deviation decreased to ± 6 2 ml or 6 2 % of the mean value

The mean *increase of the stroke volume from rest to the first work load* was 13 5 ± 8 8 ml ($P < 0.001$, $n = 16$) This increase was only related to the individual slope of cardiac output on oxygen uptake (r = 0 65**), to the blood volume (0 59*) and to the heart volume (0 57*) It was not related to the values of blood volume per kg body weight (r = 0 25) or heart volume per kg body weight (0 44)

The difference between the stroke volume at the second and the first work load (II—I) was + 2 3 ± 9 0 ml ($P > 0.3$ $n = 16$) This difference was positively related to the anamnestic degree of physical activity (b = 15**) and to the difference in pulmonary artery pulse pressure between the second and the first load (PA_{s-D}, II—I) (r = 0 60*, b = 0 84) it was negatively related to the heart rate increase from the second to the sixth minute at the *second load* (St st II r = — 0 62*, b = — 1 3) and to the heart rate at the second load (r = — 0 53* b = — 0 47) The correlation coefficients with *BA_{s-D} II—I, PVC* II—I and RV_{D}, II were 0 51 0 48 and 0 48 respectively ($P < 0.1$) Combining the degree of physical activity (b = 12**) with PA_{s-D} II—I (b = 0 60, $P < 0.02$) as independent variables the residual standard deviation decreased to ± 5 2 ml With physical activity and heart rate at the second load or physical activity and St st II the corresponding values were ± 5 6 and ± 5 7 ml, respectively

If it had been assumed that the whole difference between the stroke volume at the two work loads was due to methodological errors, the coefficient of variation for a *single* determination would have been ± 6 4 % But taking the physiological relationships into account (mainly the degree of physical activity) the remaining variance corresponded to an error of ± 3 7 % for a single determination of stroke volume during exercise

Heart rate steady state during exercise

The mean increase in heart rate from the second to the sixth minute at heart rate 130 (St st_{130}) during catheterization was 7 4 ± 3 7 beats/min (P < 0 001, n = 16) It was correlated to Log $lact_{130}$ measured before catheterization (r = 0 66**) and to PA_{S-D} II (— 0 51*) The correlation coefficients with stroke volume II—I, slope of BA_M on cardiac output and RV_{De} II were — 0 49, 0 49, — 0 48, respectively (P < 0 1), and with PVC II — 0 45 The negative regression on degree of physical activity was not of probable significance (P < 0 1) There was no correlation with the slope of cardiac output on oxygen uptake (r = 0 11) When Log $lact_{130}$ (**) and the slope of BA_M on cardiac output (*) were combined as independent variables, the residual standard deviation decreased to ± 2 4 beats/min

The mean 2—6 minute heart rate increase at the second work load was 7 6 ± 4 4 beats/min (P < 0 001, n = 16) It was correlated to the increase in heart rate from the first to the second load (r = 0 63**, b = 0 46), to the stroke volume II—I (r = — 0 62*, b = — 0 30), to the slope of BA_M on cardiac output (r = 0 57*, b = 1 6) and to Log $lact_{130}$ (r = 0 50*, b = 17) There was no correlation with the slope of cardiac output on oxygen uptake (r = 0 19) Combining stroke volume II—I (*) with the slope of BA_M (P < 0 1) or heart rate II—I (*) as independent variables, the residual standard deviation decreased to ± 3 2 — ± 3 1 beats/min

PCV pressure (fig 2)

At rest the mean PCV pressure was 9 9 ± 2 3 mm Hg (n = 16) It was positively related to *the systemic resistance* index at rest (r = 0 62*) and to heart

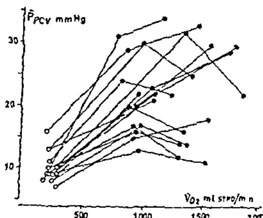


Fig 2 Mean PCV pressure ($\bar{P}_{PCV}$) in relation to oxygen uptake Symbols as in fig 1

volume (r = 0 58*, b = 0 0074), and negatively related to the slope of systolic brachial artery pressure on oxygen uptake at rest and during exercise (r = — 0 58*) *and to cardiac output at rest* (r = — 0 50*, b = — 1 1) When heart volume (**) and cardiac output at rest (*) were combined as independent variables, or heart volume and systemic RI at rest, the residual standard deviation decreased to ± 1 7 mm Hg

At the second work load the mean PCV pressure was 22 1 ± 8 1 mm Hg (n = 14) It was positively related to right ventricular end-diastolic pressure, to the pulse pressure in the pulmonary and brachial arteries and to the degree of physical activity (table IX), and negatively related to the quotient FRC/TLC, to the increase in respiratory variations of the systolic pulmonary artery pressure from the first to the second load (Resp var PA_s II—I) and to the slope of the pressure drop over the peripheral pulmonary vessels on cardiac output The correlation coefficient with heart volume was 0 49 (P < 0 1) *with the increase* of the stroke volume from the first to the second work load 0 43 with St st_{130} — 0 45 and with age 0 37

Table IX PCV pressure at the second work load (y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure RV_D II	0.81***	1.2
FRC/TLC	−0.73**	−1.1
Pressure PA_{S-D} II	0.73**	1.4
Pressure RV_{De} R	0.71**	2.8
Pressure BA_{S-D} II—I[1]	0.70**	0.74
Respir var PA_S II—I	−0.64*	−1.7
Physical activity	[2]P < 0.05	11
FEV	0.58*	0.71
Slope of Q on V_{O_2}	0.58*	5.3
V_E/V_{O_2} II—I	0.54*	1.6
Slope of (PA_M PCV_M) on $\dot{Q}$	0.54*	−8.1

[1] n = 13 [2] Significance of b

Table X Mean value of PCV pressure during exercise (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure RV_D W	0.75***	1.1
Respir var PA_S II I	0.63**	1.3
Pressure RV_{De} R	0.61*	1.8
Pressure PA_{S-D} II	0.58*	0.75
FRC TLC	−0.58*	−0.60
V_E/V_{O_2} II	0.55*	0.89
Pressure RV_S W	0.5?*	0.51
Pressure BA_{S-D} II—I	0.53*	0.45
ECG_{QRS}	P < 0.05	2.7
Physical activity	P < 0.05	6.9

n = 14 * Significance of b

Combining the right ventricular end diastolic pressure (RV_{De} II) (b = 0.96***) with Resp var PA_S II—I (b = −1.0*) as independent variables the residual standard deviation decreased to ± 4.0 mm Hg When RV_{De} II was combined with FRC/TLC it was ± 4.3 mm Hg, and when FRC/TLC was combined with age (b = 0.53*) ± 4.9 mm Hg The lowest residual standard deviation (± 2.4 mm Hg) was obtained with Respir var PA_S II I (b = −1.6***) and BA_{S-D} II—I (b = 0.76***) as independent variables

Table XI Difference between the PCV pressure at the second and the first work load (II I y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure RV_S II—I	0.75**	0.48
Pressure PA_{S-D} II—I	0.75**	0.63
Pressure BA_{S-D} II—I[1]	0.72**	0.58
Pressure RV_{De} II—I	0.71**	1.2
Level of (PA_M PCV_M) on Q	0.68**	−0.06
ECG_{VEB} (repeated)	[2]P < 0.01	−2.0
Pressure RV_{De} II	0.65**	0.67
Pressure PA_{S-D} R	0.63*	−1.6
Total haemoglobin	0.58*	0.034
Heart rate R	0.57*	0.34
Slope of (PA_M PCV_M) on Q	−0.53*	−0.57

[1] n = 13 [2] Significance of b

Table XII Right ventricular end diastolic pressure at rest (y) in relation to some anthropometric data (x) in 17 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure PCV II	0.71**	0.18
Pressure PA_{S-D} II[1]	0.62**	0.27
Pressure PA_{S-D} R	0.56*	−0.53
Pressure RV_D W[2]	0.55*	0.24
ECG_{VEB} (repeated)	P < 0.05	−0.57
Respir var PA II	−0.53*	−0.30
Respir var PA_S II—I[1]	0.51*	−0.35

[1] n = 16 [2] n = 14 * Significance of b

The *mean PCV pressure during exercise* was 22.2 ± 6.2 mm Hg (n = 16) The relationships with some other data are given in table X The correlation coefficient with heart volume was 0.49 ($P < 0.1$) and with age 0.43 When FRC/TLC (b = −0.91***) and age (b = 0.51*)

Heart rate steady state during exercise

The mean increase in heart rate from the second to the sixth minute at heart rate 130 (St st_{130}) during catheterization was 7 4 ± 3 7 beats/min (P < 0 001 n = 16) It was correlated to Log $lact_{130}$ measured before catheterization (r = 0 66**) and to PA_{S-D} II (— 0 51*) The correlation coefficients with stroke volume II—I, slope of BA_{st} on cardiac output and RV_{De} II were — 0 49, 0 49, — 0 48, respectively (P < 0 1), and with PVC II — 0 45 The negative regression on degree of physical activity was not of probable significance (P < 0 1) There was no correlation with the slope of cardiac output on oxygen uptake (r = 0 11) When Log $lact_{130}$ (**) and the slope of BA_{st} on cardiac output (*) were combined as independent variables, the residual standard deviation decreased to ± 2 4 beats/min

The mean 2—6 minute heart rate increase at the second work load was 7 6 ± 4 4 beats/min (P < 0 001, n = 16) It was correlated to the increase in heart rate from the first to the second load (r = 0 63**, b = 0 46), to the stroke volume II—I (r = — 0 62*, b = — 0 30), to the slope of BA_{st} on cardiac output (r = 0 57*, b = 1 6) and to Log $lact_{130}$ (r = 0 50*, b = 17) There was no correlation with the slope of cardiac output on oxygen uptake (r = 0 19) Combining stroke volume II—I (*) with the slope of BA_{st} (P < 0 1) or heart rate II—I (*) as independent variables, the residual standard deviation decreased to ± 3 2 — ± 3 1 beats/min

PCV pressure (fig 2)

At rest the mean PCV pressure was 9 9 ± 2 3 mm Hg (n = 16) It was positively related to the systemic resistance index at rest (r = 0 62*) and to heart

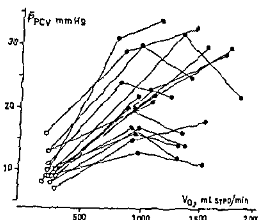


Fig 2 Mean PCV pressure ($\bar{P}_{PCV}$) in relation to oxygen uptake Symbols as in fig 1

volume (r = 0 58*, b = 0 0074), and negatively related to the slope of systolic brachial artery pressure on oxygen uptake at rest and during exercise (r = — 0 58*) and to cardiac output at rest (r = — 0 50*, b = — 1 1) When heart volume (**) and cardiac output at rest (*) were combined as independent variables, or heart volume and systemic RI at rest, the residual standard deviation decreased to ± 1 7 mm Hg

At the second work load the mean PCV pressure was 22 1 ± 8 1 mm Hg (n = 14) It was positively related to right ventricular end-diastolic pressure, to the pulse pressure in the pulmonary and brachial arteries and to the degree of physical activity (table IX), and negatively related to the quotient FRC/TLC, to the increase in respiratory variations of the systolic pulmonary artery pressure from the first to the second load (Resp var PA_S II—I) and to the slope of the pressure drop over the peripheral pulmonary vessels on cardiac output The correlation coefficient with heart volume was 0 49 (P < 0 1) with the increase of the stroke volume from the first to the second work load 0 43, with St st_{130} — 0 45 and with age 0 37

Table IX PCV pressure at the second work load (y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure RV$_D$ II	0.81***	1.2
FRC/TLC	−0.73**	−1.1
Pressure PA$_{S-D}$ II	0.73**	1.4
Pressure RV$_D$ R	0.71**	2.8
Pressure BA$_{S-D}$ II—I¹	0.70**	0.74
Resp var PA$_S$ II—I	−0.64*	−1.7
Physical activity	*P<0.05	11
FEV %	0.58*	0.71
Slope of Q on $\dot{V}_{O_2}$	0.58*	5.3
$\dot{V}_E/\dot{V}_{O_2}$ II—I	0.54*	1.6
Slope of (PA$_M$ PCV$_M$) on $\dot{Q}$	−0.54*	8.1

¹ n = 13 * Significance of b

Table X Mean value of PCV pressure during exercise (y) in relation to some anthropometric data (x) in 16 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure RV$_{De}$ W	0.75***	1.1
Resp var PA$_S$ II—I	0.65**	1.3
Pressure RV$_{De}$ R	0.61*	1.8
Pressure PA$_{S-D}$ II	0.58*	0.75
FRC/TLC	0.58*	0.60
$\dot{V}_E/\dot{V}_O$ II	0.55*	0.89
Pressure RV$_S$ W	0.53*	0.51
Pressure BA$_{S-D}$ II—I	0.53*	0.45
ECG$_{QRS}$	*P<0.05	2.7
Physical activity	*P<0.05	6.9

n 14 * Significance of b

Combining the right ventricular end diastolic pressure RV$_{De}$ II) (b = 0.96***) with Resp var PA$_S$ II—I (b = −1.0*) as independent variables the residual standard deviation decreased to ± 4.0 mm Hg When RV$_{De}$ II was combined with FRC/TLC it was ± 4.3 mm Hg and when FRC/TLC was combined with age (b = 0.53*) ± 4.9 mm

Table XI Difference between the PCV pressure at the second and the first work load (II I, y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure RV$_S$ II—I	0.75**	0.48
Pressure PA$_S$ D II—I	0.75**	0.63
Pressure BA$_{S-D}$ II—I¹	0.72**	0.58
Pressure RV$_D$ II—I	0.71**	1.2
Level of (PA$_M$ PCV$_M$) on Q	−0.68**	−0.96
ECG$_{VEB}$ (repeated)	*P<0.01	−2.0
Pressure RV$_D$ II	0.65**	0.67
Pressure PA$_{S-D}$ R	−0.63*	−1.6
Total haemoglobin	0.58*	0.034
Heart rate R	0.57*	0.34
Slope of (PA$_M$ PCV$_M$) on Q	−0.53*	−0.57

¹ n = 13 * Significance of b

Table XII Right ventricular end-diastolic pressure at rest (y) in relation to some anthropometric data (x) in 17 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure PCV II¹	0.71**	0.18
Pressure PA$_S$ D II	0.62**	0.27
Pressure PA$_{S-D}$ R	0.56*	−0.53
Pressure RV$_{De}$ W²	0.55*	0.24
ECG$_{VEB}$ (repeated)	*P<0.05	−0.57
Resp var PA$_S$ II	−0.53*	−0.30
Resp var PA$_S$ II—I¹	−0.51*	−0.35

¹ n 16 ² n = 14 * Significance of b

Hg The lowest residual standard deviation (± 2.4 mm Hg) was obtained with Respir var PA$_S$ II—I (b = −1.6***) and BA$_{S-D}$ II—I (b = 0.76***) as independent variables

The *mean PCV pressure during exercise* was 22.2 ± 6.2 mm Hg (n = 16) The relationships with some other data are given in table X The correlation coefficient with heart volume was 0.49 (P < 0.1) and with age 0.43 When FRC/TLC (b = −0.91***) and age (b = 0.51*)

Heart rate steady state during exercise

The mean increase in heart rate from the second to the sixth minute at heart rate 130 (St st_{130}) during catheterization was 7 4 ± 3 7 beats/min ($P < 0\ 001$, $n = 16$) It was correlated to Log $lact_{130}$ measured before catheterization ($r = 0\ 66^{**}$) and to PA_{S-D} II (— 0 51*) The correlation coefficients with stroke volume II—I, slope of BA_M on cardiac output and RV_{De} II were — 0 49, 0 49, — 0 48, respectively ($P < 0\ 1$), and with PVC II — 0 45 The negative regression on degree of physical activity was not of probable significance ($P < 0\ 1$) There was no correlation with the slope of cardiac output on oxygen uptake ($r = 0\ 11$) When Log $lact_{130}$ (**) and the slope of BA_M on cardiac output (*) were combined as independent variables, the residual standard deviation decreased to ± 2 4 beats/min

The mean 2—6 minute heart rate increase at the second work load was 7 6 ± 4 4 beats/min ($P < 0\ 001$, $n = 16$) It was correlated to the increase in heart rate from the first to the second load ($r = 0\ 63^{**}$, $b = 0\ 46$), to the stroke volume II—I ($r = -0\ 62^*$, $b = -0\ 30$), to the slope of BA_M on cardiac output ($r = 0\ 57^*$, $b = 1\ 6$) and to Log $lact_{130}$ ($r = 0\ 50^*$, $b = 17$) There was no correlation with the slope of cardiac output on oxygen uptake ($r = 0\ 19$) Combining stroke volume II—I (*) with the slope of BA_M ($P < 0\ 1$) or heart rate II—I (*) as independent variables, the residual standard deviation decreased to ± 3 2 — ± 3 1 beats/min

PCV pressure (fig 2)

At rest the mean PCV pressure was 9 9 ± 2 3 *mm* Hg ($n = 16$) It was positively related to the systemic resistance index at rest ($r = 0\ 62^*$) and to heart

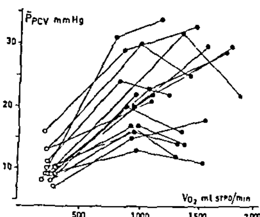


Fig 2 Mean PCV pressure ($\bar{P}_{PCV}$) in relation to oxygen uptake Symbols as in fig 1

volume ($r = 0\ 58^*$, $b = 0\ 0074$), and negatively related to the slope of systolic brachial artery pressure on oxygen uptake at rest and during exercise ($r = -0\ 58^*$) and to cardiac output at rest ($r = -0\ 50^*$, $b = -1\ 1$) When heart volume (**) and cardiac output at rest (*) were combined as independent variables, or heart volume and systemic RI at rest, the residual standard deviation decreased to ± 1 7 mm Hg

At the second work load the mean PCV pressure was 22 1 ± 8 1 mm Hg ($n = 14$) It was positively related to right ventricular end-diastolic pressure, to the pulse pressure in the pulmonary and brachial arteries and to the degree of physical activity (table IX), and negatively related to the quotient FRC/TLC, to the increase in respiratory variations of the systolic pulmonary artery pressure from the first to the second load (Resp var PA_S II—I) and to the slope of the pressure drop over the peripheral pulmonary vessels on cardiac output The correlation coefficient with heart volume was 0 49 ($P < 0\ 1$) with the increase of the stroke volume from the first to the second work load 0 43, with St st_{130} — 0 45 and with age 0 37

Table XIII Right ventricular end-diastolic pressure at the second work load (y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure PAs_{-D} II	0.86***	1 1
Pressure PCV II	0 81***	0 5?
Pressure PAs_{-D} II I[1]	0 74**	0 52
Pressure RVs II	0 71**	0 47
V_E/V_O II—I	0 65*	1 3
ECG_{QRS}	P< 0 025	2 6
FRC/TLC	−0 56*	−0 58
FEV °	0 54*	0 45

[1] n = 13 * Significance of b

Table XIV Mean value of right ventricular end diastolic pressure during exercise (y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure PAs_{-D} II	0.82***	0 89
Pressure PCV II	0 81***	0 47
V_E/V_{O_2} II—I	0 73**	1 3
Pressure BAs_{-D} II—I	0 70**	0 41
Pressure RVs II	0 69**	0 39
V_E/V_{O_2} II	0 62*	0 72
FRC/TLC	−0 58*	−0 51
V_E II	0 57*	0.27
RV/TLC	−0 56*	−0.80
Pressure RV_D R	0 55*	1 3

n = 13

Table XV Increase of right ventricular end-diastolic pressure from rest to first work load (y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
V_E/V_O II	0 71**	0 57
Pressure RVs W	0 68**	0 32
V_E II	0 60*	0 22
Pressure RVs I—R	0 66*	0.28
V_E/V_{O_2} II—I	0 61*	0 74
Pressure PAs_{-D} I—R	0 57*	0 42
Pressure PCV I—R	0 56*	0 32

Table XVI Difference between right ventricular end diastolic pressure at the second and the first work load (II I y) in relation to some anthropometric data (x) in 14 old men Symbols as in table III and under Methods

Independent variable	r	b
Pressure PAs_{-D} II—I	0 77**	0 38
Pressure RVs II—I	0 76**	0 29
V_E/V_{O_2} R	0 72**	0 48
Pressure PCV II—I	0 71**	0 42
Pressure PAs_{-D} II	0 67**	0 52
V_E R	0 62*	1 0
Pressure BAs_{-D} II—I[1]	0 59*	0.27
ECG_{QRS}	*P< 0 025	1 6
Physical activity (earlier)	*P< 0 05	3.2
Log $lact_{130}$	−0 58*	−0 14
Heart rate R	0 58*	0 21

n = 13 * Significance of b

nificantly related to the RV systolic pressure (table XIV) It was negatively related (P < 0 05) to the quotients FRC/TLC and RV/TLC (table XIV) When the PCV pressure at the second load (*) was combined with PA_{-D} II(*) or PCV II (**) with the slope of BA_M on cardiac output (*), the residual standard deviation was ± 2 4 mm Hg

The mean *increase of RV_{D} pressure from rest to the first work load* was 5 2 ± 3 2 mm Hg (P < 0 001 n = 14) It was positively correlated to the total ventilation at the second load and more so with the ventilation per l oxygen uptake (table XV) Furthermore it was related to the simultaneous increases in the RV systolic and the PCV pressure as well as to the increase in pulmonary artery pulse pressure (table XV) When V_E/V_{O_2} (b = 0 49**) and PAs_{-D} I—R (b = 0 30*) were combined as independent variables, the residual standard deviation decreased to ± 2 0 mm Hg

were combined as independent variables, the residual standard deviation was ± 4 3 mm Hg, when Resp var PA_S II—I was combined with V_t/V_{O_2} at the second load it was 3 5 mm Hg The lowest residual SD (± 2 2 mm Hg) was obtained with Resp var PA_S II—I (b = — 1 4***) and BA_{S-D} II—I (b = 0 50***) as independent variables

The *mean increase of the PCV pressure from rest to the first work load* was 12 1 ± 5 4 mm Hg ($P < 0\,001$, n = 16) This increase was only related to V_t/V_{O_2} at the second load (r = 0 57*) and to the increases of the right ventricular end-diastolic (r = 0 56*) and systolic pressures (0 53*)from rest to the first load

The difference between the PCV pressure at the second and the first work load (II—I) was 0 07 ± 5 7 mm Hg ($P > 0\,9$, n = 14) This difference was significantly related to simultaneous changes in right ventricular systolic and end diastolic pressures and to changes of the pulse pressures in the pulmonary and brachial arteries (table X) The correlation coefficient with simultaneous changes of the stroke volume was 0 48 ($P < 0\,1$) The difference was also significantly negatively related to the classification of ventricular ectopic beats during previous repeated exercise tests (table X) Combining RV_S II—I (**) with ECG_{VEB} (repeated) (*) or with total haemoglobin (*) as independent variables, and PA_{S-D} II—I (**) with total haemoglobin (*) or with heart rate at rest(*), the residual standard deviations decreased to ± 3 2 — ± 3 4 mm Hg

Right ventricular end diastolic pressure (RV_{De}) (fig 3)

At rest The mean RV_{De} pressure was 8 1 ± 2 0 mm Hg (n = 17), and the relationships with some other data are given

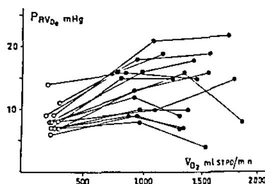


Fig 3 Right ventricular end-diastolic pressure (P_{RVDe}) in relation to oxygen uptake Symbols as in fig 1

in table XII When the PCV pressure at the second load (**) and the pressure in the pulmonary artery at rest(*) were combined as independent variables, the residual SD decreased to ± 1 2 mm Hg

At the second work load the mean RV_{De} pressure was 13 1 ± 5 6 mm Hg (n = 14) It was significantly related to the pulse pressure in the pulmonary artery, the PCV pressure and the RV systolic pressure at the second load (table XIII) It was negatively related to the quotient FRC/TLC and positively to $FEV_{\%}$ (table XIII) When the PCV pressure at the second load ($P < 0\,1$) was combined with PA_{S-D} II (**), and when PCV II (**) was combined with the slope of BA_M on cardiac output (*) or PCV II (*) with both the slope of BA_M on cardiac output (**) and the residual volume (b = — 4 3*) as independent variables the residual standard deviations decreased to ± 2 6, ± 2 9 and ± 2 4 mm Hg, respectively The lowest residual standard deviation (± 2 1 mm Hg) was obtained with PA_{S-D} II (**) and BA_{S-D} II—I (*) as independent variables

The *mean RV_{De} pressure during exercise* was 13 6 ± 4 7 mm Hg (n = 14) It was highly significantly related to the pulmonary artery pulse pressure and to the PCV pressure at the second load, and sig

W_{max} in this group of old men was better related to peripheral circulatory, muscular or metabolic than to central circulatory factors

HR_{max} was not primarily related to any of the catheterization data except the heart rate at the second work load (r = 0 70**)

Discussion

Effect of deviation from 'basal conditions on circulatory findings

In the presently studied group of old men the interindividual variations in the increase of oxygen uptake at rest above the predicted basal values were associated with variations in oxygen uptake (r — 0 66**) heart rate (0 65**) and cardiac output at rest (0 52*) There was, however, no correlation of probable significance with stroke volume (0 11) or arterio venous oxygen difference at rest (— 0 14), nor with the PCV, right ventricular pulmonary or brachial artery pressures at rest The heart rate at rest was positively correlated to oxygen uptake (r = 0 81***) and cardiac output at rest (0 70**) but not to slope or level of cardiac output on oxygen uptake or to stroke volume or arterio-venous oxygen difference at rest

Individual responses at rest to experimentally induced alterations of affect were investigated in young men by Bogdonoff et al (4) In their group of subjects with marked anxiety and most probably a marked increase of the metabolic rate the cardiac output increased 63 % both by increase of heart rate (28 %) and of stroke volume (26 %) Simultaneously the brachial artery systolic pressure increased 20 mm Hg

The correlation between the increase of oxygen uptake above the predicted basal values and the slope of cardiac output on oxygen uptake was negative, and the correlation with the level of cardiac output on oxygen uptake was not of probable significance (— 0 20) There were thus no signs in the present study that the deviation from predicted basal oxygen uptake at rest was also associated with increased cardiac output during exercise

Cardiac output and arterio venous difference

The cardiac output at rest could not be shown to be related to body size in the present material as it was in a material of young men (23) This may be attributed to the variations in respect of basal conditions, which significantly influenced the cardiac output at rest in this study, or to the differences in age between the materials Nor could the cardiac output at rest be shown to be related to age, heart volume or degree of abnormality of electrocardiographic findings during exercise tests

The subjects with the highest arterio venous oxygen differences and thus the most pronounced hypokinetic circulation at rest were also more hypokinetic during exercise than the others They also had lower stroke volumes at rest and during exercise than the others The relationship between stroke volume and arterio-venous oxygen difference at rest was further evidenced by the fact that neither of these variables was found to be correlated to heart rate oxygen uptake or increase of oxygen uptake at rest above the predicted basal value

Within the group of old men the subjects with the largest heart volumes at rest and the highest PCV pressures at the second work load showed a higher increase of cardiac output during exercise in relation to the increase of oxygen uptake than the others The lower values of

Table VIII Some relationships with PCV and right ventricular end-diastolic pressures at rest and during exercise in 17 old men + denotes positive correlation or regression coefficient of at least probable significance — denotes corresponding negative coefficients Other symbols are explained under Methods

	PCV pressure					RV De pressure				
	R	II	W	I R	II I	R	II	W	I R	II I
Heart volume	+									
ECG_{QRS}			+				+			–
ECG_{VEB} (repeated)					–	–				
FRC/TLC		–	–				–	–		
RV/TLC								–		
$FEV_{\%}$		+					+			
V_E/V_O II			+							
V_E/V_{O_2} II I		+					+	+	+	
Respir var PAs, II I		–	–			–				
Physical activity		+	+							–
$Log\ lact_{130}$										–

The difference between RV_{De} pressure at the second and the first work load (II—I) was -0.4 ± 3.3 mm Hg ($P > 0.6$, $n = 14$) It was related to the simultaneous changes in the RV systolic and the PCV pressure and to the changes in pulse pressure in the pulmonary and brachial arteries (table XVI) It was also positively related to the degree of physical activity and negatively to Log $lact_{130}$ (table XVI) When PCV II—I (**) was combined with Log $lact_{130}$ (*), PVC II—I (*) with V_E/V_{O_2} R (*) or PCV II—I (**) with ECG_{QRS} (*) as independent variables, the residual standard deviation was $\pm 2.0 - \pm 2.1$ mm Hg The lowest residual standard deviation (± 1.8 mm Hg) was obtained with RV_S II—I (**) and PA_{S-D} II ($P < 0.02$) as independent variables

Work load and heart rate at maximal working intensity (W_{max}, HR_{max})

W_{max} in sitting position at repeated exercise tests before catheterization was on an average 851 ± 162 kpm/min ($n = 17$) The only relationships obtained between W_{max} and the data from catheterization in supine position were with oxygen uptake at the second work load ($r = 0.87$***), stroke volume at the second load (0.59*) and oxygen uptake at rest (0.55*) The correlation coefficient between W_{max} in supine position and stroke volume at the second load was 0.50 ($P < 0.1$)

In a previous study of a larger group of old men (21) it was observed that the two best independent variables for predicting W_{max} were Log $lact_{600}$ and age In the present study the correlation coefficients between W_{max} and Log $lact_{600}$, age and stroke volume II were -0.84***, -0.52 and 0.59*, respectively The correlation coefficient between Log $lact_{600}$ and stroke volume II was -0.62* The partial correlation coefficient between W_{max} and Log $lact_{600}$ was -0.77** after eliminating the influence of the two other variables, the corresponding partial correlation coefficients between W_{max} and age and between W_{max} and stroke volume at the second load were -0.54 and 0.11, respectively In agreement with previous findings (21) this should suggest that

crease of dimensions of the cardiovascular system induced by training, but more with regulation of the distribution of blood volume during exercise and presumably with the ability to increase the central blood volume during exercise

The standard deviation of the difference between stroke volume at the first and the second work load in the present study ($\pm$ 9 0 ml) corresponds to the error of a single determination of stroke volume during exercise ($\pm$ 6 8 %) obtained from duplicate determination at the same work load in a mixed material of heart and lung patients (13) In the present study almost half of this variation was found to be associated with physiological variation in the procedure for duplicate determinations, which could best be accounted for by the two independent variables, degree of physical activity and simultaneous changes in pulmonary artery pulse pressure The remaining variance corresponded to an error of only $\pm$ 3 7 % for a single determination of stroke volume during exercise

Pressure

Within this material no primary correlation could be proved between age and the PVC or right ventricular end diastolic pressures (RV_D), either at rest or during exercise nor to the increase from rest to exercise The effects of some other variables on the filling pressure at rest and during exercise are summarized in table XVII Neither the total assessment of the eletrocardiographic findings nor the assessment of the ST segment or the supraventricular beats were related to any of the pressures The pressures during exercise were not related to heart volume

The subjects with high scores for ECG QRS of whom three cases had so called peri infarction block, thus had higher filling pressures during exercise than the others, whereas the cases with frequent ventricular ectopic beats at previous repeated tests had a lower than average increase of the PCV pressure from the first to the second load

The higher PCV pressures during exercise and the higher increases of the right ventricular end diastolic pressures during exercise in the subjects with the higher scores for anamnestic degree of physical activity, are in accordance with the suggestion above, that these cases had a more marked increase of the central blood volume during exercise

The pulmonary ventilatory function was positively correlated to the filling pressures during exercise High values for the quotients FRC/TLC and RV/TLC and low values for FEV% were thus associated with low values for PCV and right ventricular end diastolic pressures during exercise as were high increases during exercise of the respiratory variations of the pulmonary artery systolic pressure This last parameter was negatively correlated to FEV% (r = − 0 63*) As the mean intrathoracic pressure during exercise should be expected to be higher than average rather than lower *in the* cases with marked respiratory pressure variations the low values for PCV and RV_D pressures should also *correspond to* low *effective* filling pressure The relationship between pulmonary ventilation and filling pressures during exercises was further evidenced by the fact that the subjects with the most marked increases from the first to the second load of the total ventilation in relation to oxygen uptake (V_E/V_O II—I) had higher right ventricular end diastolic pressures ($P < 0.005$) and also higher PCV pressures ($P < 0.05$) than the others

A relationship between the increase in

cardiac output at rest and during exercise and the higher filling pressures during exercise, in these old men compared to previously studied young men (2, 12) were thus not signs of heart failure

Stroke volume

The variations in stroke volume at rest could not be shown to be related to age, heart volume or electrocardiographic findings, and hardly at all to the various measurements of body size, only slightly to height The stroke volume during exercise, however, was significantly related to blood volume and body size measured as body surface area and to a probable significant extent to heart volume and work load at maximal performance By combining blood volume with maximal voluntary ventilation as independent variables the residual standard deviation for prediction of stroke volume at the second work load from these variables was only ± 5 2 %, i e half of the original standard deviation

The changes in stroke volume from the first to the second load were accompanied by simultaneous changes ($P < 0\ 05$) of the pulse pressure in the pulmonary artery and less so ($P < 0\ 1$) by changes in PCV pressure and pulse pressure in the brachial artery Although there occurred no significant mean change of the stroke volume, the individual changes thus seemed to be due to real physiological variation and not solely to methodological errors

The decrease in stroke volume from the first to the second work load was positively related to the 2—6 minute heart rate increase at the second load This decrease in stroke volume may be supposed to have occurred during exercise at the second load, as it was shown by Donald et al (6) that cardiac output was constant from the first to the fifth minute of exercise at constant load This suggestion is also supported by the findings during prolonged exercise in young men (7), when an increase of heart rate at constant work load was found to be associated with a decrease of the stroke volume

The significant and positive relationship between the anamnestic degree of physical activity and the increase in stroke volume from the first to the second load agrees with the observations of Granath et al (10) Thus in three of the presently studied old men (case nos 8, 69b and 69c) intense physical training for 3—4 weeks increased the mean stroke volume at the second load in supine position by 8 %, whereas the mean stroke volumes at rest and at the first load in supine position were unchanged In sitting position the mean stroke volume increased by 8—12 % at the first and second work loads This effect of intense physical training on the increase of the stroke volume during supine exercise might also explain why the subjects studied by Bevegård et al (1), who where trained for 2 weeks prior to catheterization, increased their stroke volume from rest to the second work load by as much as 28 %, compared to 5—10 % earlier observed in ordinarily trained young men (2, 12) The athletes studied by Bevegard et al (3) increased their mean stroke volume from rest to the second load by only 16 %, yet in their own opinion they were in a state of only medium fitness The fact that their mean oxygen uptake at rest deviated more from the predicted basal values than in the group of ordinarily trained young men may also have influenced upon this figure It thus may seem as though the effect of physical activity and training on the increase of the stroke volume during supine exercise was associated not with the in-

blood volume, body surface area, working intensity at heart rate 130 and at maximal performance, heart volume, vital capacity and maximal voluntary ventilation (MVV) and in those with the most abnormal ECG_{ST} When blood volume and MVV were combined as independent variables, the residual standard deviation for stroke volume during exercise decreased to $\pm 5.2\%$

7 The increase in stroke volume from the first to the second work load was positively influenced by the degree of physical activity according to case history and negatively by the increase in heart rate from the second to the sixth minute at the second load The residual standard deviation corresponded to an error for a single determination of stroke volume during exercise of $\pm 3.7\%$

8 The PCV pressure and the right ventricular end-diastolic (RV_{De}) pressure during exercise were positively related to degree of physical activity and to degree of abnormality of the QRS complexes in the ECG The increase of the PCV pressure during exercise was lower in the cases with frequent ventricular ectopic beats than in the others

9 The pulmonary ventilatory function significantly and positively influenced the PCV and RV_D pressures during exercise The lowest pressures during exercise were observed in the cases with the highest values for FRC/TLC and RV/TLC, the lowest values for FEV % and the most marked increases during exercise of the respiratory variations in the pulmonary artery systolic pressure i e in cases in which the highest airway resistances could be expected

10 Individual changes in PCV and RV_{De} pressures during exercise were associated with corresponding changes of arterial pulse pressures during exercise and thus the ventricles of these old men seemed to function in accordance with Starling's law of the heart

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respiratory rate and heart rate during exercise after acute bleeding was observed by Gullbring et al (11) and it was suggested that increase in respiratory rate and ventilation during exercise after bleeding might be a compensatory mechanism due to the acute decrease in blood volume

The relationships discussed above together with the significant positive correlation observed between maximal voluntary ventilation and stroke volume at the second load suggest that the variation of the pulmonary ventilatory function within this material affected the filling pressures of the heart during exercise through variations of the central blood volume For it has been observed that intermittent positive pressure breathing at rest in supine position decreases the cardiac output (24), and that pressure breathing in this position is accompanied by blood volume displacements out from the thorax (8) Moreover, during positive pressure breathing in dogs, the decrease in cardiac output was accompanied by a decrease of central blood volume (5) Marked ventilatory expiratory obstruction during steady-state exercise has been shown to cause a decrease of cardiac output and central blood volume (15) In the present group of old men it seems as if the effect of the ventilatory function on the circulation during exercise should be more pronounced regarding filling pressures than cardiac output and stroke volume In agreement with this, normal values for cardiac output and stroke volume during exercise were generally recorded in a material of 50 year old men with pulmonary emphysema, whereas the PCV pressures during exercise were low (14)

As there was a positive relationship between the individual changes during exercise in filling pressures and arterial pulse pressures, the right and left ventricle of these old men seemed to function in accordance with Starling's law of the heart The relationships between changes in filling pressures during exercise and changes in stroke volume were also positive but less significant ($P < 0.1$) Thus the external work per heart beat (volume × pressure) also increased when the filling pressures increased

Summary

1 Seventeen healthy males aged 61—83 years, were studied by right heart catheterization at rest and at two loads in supine position

2 Cardiac output at rest could not be shown to be related to body size or age It was, however, positively correlated to heart rate and to increase in oxygen uptake above predicted basal values, indicating the importance of "basal" conditions

3 During exercise the cardiac output increased more in relation to oxygen uptake in the cases with large heart volumes at rest and high PCV pressures during exercise This indicates that no heart failure was present

4 Cases with small stroke volume, blood volume and heart volume, low weight and normal ST segment in the exercise ECG (ECG_{ST}) had a lower cardiac output in relation to oxygen uptake than the others when values at rest and during exercise were considered together

5 Stroke volume at rest was more negatively correlated to the arterio-venous oxygen difference than it was positively correlated to the oxygen pulse It could not be shown to be related to heart rate or oxygen uptake

6 Stroke volume during exercise was higher in the cases with high values of

blood volume, body surface area, working intensity at heart rate 130 and at maximal performance, heart volume, vital capacity and maximal voluntary ventilation (MVV), and in those with the most abnormal ECG_{ST}. When blood volume and MVV were combined as independent variables, the residual standard deviation for stroke volume during exercise decreased to ± 5.2 %.

7. The increase in stroke volume from the first to the second work load was positively influenced by the degree of physical activity according to case history and negatively by the increase in heart rate from the second to the sixth minute at the second load. The residual standard deviation corresponded to an error for a single determination of stroke volume during exercise of ± 3.7 %.

8. The PCV pressure and the right ventricular end diastolic (RV_D) pressure during exercise were positively related to degree of physical activity and to degree of abnormality of the QRS complexes in the ECG. The increase of the PCV pressure during exercise was lower in the cases with frequent ventricular ectopic beats than in the others.

9. The pulmonary ventilatory function significantly and positively influenced the PCV and RV_{D} pressures during exercise. The lowest pressures during exercise were observed in the cases with the highest values for FRC/TLC and RV/TLC, the lowest values for FEV% and the most marked increases during exercise of the respiratory variation in the pulmonary artery systolic pressure, i.e. in cases in which the highest airway resistances could be expected.

10. Individual changes in PCV and RV_{D} pressures during exercise were associated with corresponding changes of arterial pulse pressures during exercise and thus the ventricles of these old men seemed to function in accordance with Starling's law of the heart.

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Gastric "Stress" Ulceration in Myocardial Infarction

By

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Acute pathological mucosal changes with bleeding and ulceration of the upper gastrointestinal tract have been reported following different stress diseases or conditions

In 1842 Curling (4) described acute ulceration in the duodenum following severe burns During the following years many reports have been published regarding gastrointestinal haemorrhage as a complication in surgical operations especially in brain and heart operations (2, 5 12)

Drugs such as cortisone and ACTH (7) adrenaline and particularly epinephrine are well known to be the cause of bleeding in the gastrointestinal tract when used in the treatment of shock patients with infusions of norepinephrine (11) Simultaneous infusions of hydrocortisone seem to worsen the vascular impairment of norepinephrine by increasing the secretion of pepsin into the gastric juice thus causing ulceration in the gastric mucosa (14)

Selye described gastrointestinal bleeding or ulceration as an important part of the alarm reaction in stress conditions following many different releasing causes The best known is the gastric stress ulceration induced by the air raids on London in 1943 (17)

Although acute myocardial infarction is a frequent disease which produces stress, few reports have been published concerning gastrointestinal bleeding or ulceration following infarctions In 1959 Katz (9) published 25 cases of duodenal haemorrhage in patients with acute myocardial infarction Twenty one of the patients died of shock Shipp et al (19) described six cases of peptic ulcers as serious complications in cases of acute infarctions Perforation occurred in four, and bleeding in two Five out of six patients died

Material

The present study comprises a total of 13 cases of gastric haemorrhage in patients with acute myocardial infarction The cases are from the 6-year period 1954—1959 during which time 1392 patients were admitted with myocardial infarction Out of these 347 patients died (40 7 %)

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TABLE II Clinical state and anti shock treatment in 11 patients in the period before death and in two surviving patients

Case	Shock	Clinical condition/analgesics	Duration of norepinephrine administration
1	No	Wailing with pain	None
2	Yes	Violent pain	1 hr
3	No	Evoked by pain/pethidine	None
4	Yes	Persistent pain	4 hrs
5	No	Morphine several times daily	None
6	Yes	Moderate pain	24 hrs
7	No	Poor condition and much pain	None
8	No	Pethidine several times daily	None
9	Yes	Severe pain	15 min
10	Yes	Much pain	18 and 6 hrs
11	Yes	Violent pain restless	None
12	No	Severe pain	None
13	No	Violent pain	None

TABLE III Post mortem findings in 11 patients at autopsy

Case	Macroscopical appearance of gastric mucosa	Amount of gastric blood
1	Several superficial ulcerations	About 150 ml
2	Numerous flat submucosal bleedings (fig 1)	None
3	Multiple mucosae erosions	None
4	Widespread petechial bleeding	Stomach full
5	One or two minor ulcerations	Great deal
6	Minor area with tiny haemorrhages	None
7	No findings died 9 days after haematemesis	None
8	Spots with tiny haemorrhages	None
9	Heavy haemorrhagic appearance one 15 × 15 mm ulcer	300 – 500 ml
10	Areas with tiny spotted mucosal haemorrhages	None
11	4 × 8 cm area of haematoma like mucosa bleeding	None

binations At the time of bleeding only three of the p-p values (Owren s method) were in the therapeutical area 11 12 and 19 % and in no case was the value below the lower limit of 10 % where treatment was considered in advisable Thus the haemorrhage is not considered to have been caused directly by the effect of coumarin

Patient no 6 treated with dicumarol had developed a haematoma after a subcutaneous injection one week before death As the p-p value was then at its lowest value (5 %) vitamin K was administered and that raised the p-p value to 50 % This was the last p-p determination before the patient died

Case no 6 was under long term anticoagulation treatment Two years after the first infarction he was admitted with a new myocardial infarct

The five patients still under the influence of heparin might possibly have had an increased tendence to bleed an impression which was further supported by the fact that in three of these patients clinical bleeding with haematemesis could be demonstrated

Case no 5 — a 70 year-old gardener — had injections of heparin 20 000 i u given subcutaneously twice a day A determination of the bleeding time showed this to be over one hour

The remaining patients had been given two or three intravenous injections of 10 000 i u rapidly acting heparin

In the other heparin treated patients so long a period had elapsed between cessation of heparin treatment and the gastric haemorrhage that any effect of the heparin must be excluded

As regards the five patients with clinical bleeding ulcers (cases 1 3 7, 12 and 13) three

TABLE I Age, sex, location of myocardial infarction, previous history of gastric ulcer details on anticoagulation with p-p%, and survivals in 13 patients with myocardial infarction

Case	Age	Sex	Location of infarction	Clinical manifestation of ulcer	Previous history of ulcer	Anticoagulation when bleeding	Interval between heparin and bleeding	p-p% when bleeding	Survival
1	83	♀	Posterior	Haematemesis	No	No	—	?	No
2	72	♀	Posterior	No	?	No	—	?	No
3	73	♂	Anterior	Melaena	No	Marcoumar	23 days	11	No
4	73	♂	Posterior	No	No	No	—	49	No
5	70	♂	Anterior	No	No	Heparin	—	85	No
6	67	♂	Posterior	No	No	Dicumarol	31 days	50	No
7	67	♂	Anterior	Haematemesis	No	Heparin + Marcoumar	—	86	No
8	63	♂	Posterior	No	No	Marcoumar	2 years	12	No
9	57	♂	Posterior	No	No	Heparin + Marcoumar	—	27	No
10	54	♂	Anterior	No	No	Marcoumar	2 days	19	No
11	43	♂	Anterior	No	?	No	—	?	No
12	69	♂	Anterior	Haematemesis	No	Heparin + Dicumarol	—	36	Yes
13	54	♂	Posterior	Haematemesis	No	Heparin + Dicumarol	—	69	Yes

Table I gives details of the patients 2 females aged 83 and 72 years and 11 males aged 43 to 73 The two females and 9 of the males died and were examined at autopsy In all cases the diagnosis of acute myocardial infarction was verified by a typical clinical sequence, electrocardiogram abnormalities, and where autopsy was performed by pathoanatomical findings Six anterior and seven posterior infarctions were found

In five patients haematemesis or melaena was present as clinical evidence of gastric bleeding during the acute phase of myocardial infarction None of these patients had any previous history of gastroduodenal ulcers However, two patients were suffering from shock and in such a poor state that it was impossible to get information regarding previous ulcers They died a few hours after admission In the remaining eight patients bleeding was found on autopsy

Two patients had experienced symptoms of gastric ulcers previously The first (case 9) a 57-year old director, had been in hospital 24 years earlier with a juxtapylonc ulcer, but during the last 18 years before the present admission he had no gastric complaints at all

The second patient (case 10), a 54 year-old hairdresser, had been admitted to another hospital 14 years previously suffering from gastritis Since then it had not been necessary for him to diet and during recent years he had no dyspepsia at all

None of the other patients had dyspeptic complaints and during their stay in hospital they showed no symptoms of actual gastric haemorrhage

Anticoagulation was initiated in nine patients Table I shows the anticoagulant drug chosen when heamorrhage was seen in the patients Heparin marcoumar or dicumarol was used, either alone or in different com

traction of a muscular sphincter around the vena hepatica takes place, thus causing stasis and secondary haemorrhage (6) It has been demonstrated later (20) that spasms in the vena hepatica can be provoked by anaphylactic shock, digitoxin, histamine and anoxia

A neurogenic mechanism as a contributary cause of acute and chronic ulcerations in the upper part of the gastrointestinal tract has also been discussed This finds support in the protective effect of vagotomia following experimentally induced ulceration by electrical (1) or chemical (10) stimulation

A more recent theory supposes a humoral factor (8, 13, 18) secreted in the hypothalamus and activating the hypophyseal secretion of ACTH with a subsequent stimulation of adrenal corticoteroid production This again stimulates the acid and pepsin secretion in the gastric mucosa, resulting in the ultimate formation of ulcer

According to Selye's theory (16) the alarm reaction in shock provokes acute gastrointestinal ulcerations among other reactions However, these heal very quickly and are the result of either an intense autonomic secretion in the splanchnic area or the release of a histamine like substance with toxic effect on the gastrointestinal mucosa (16)

It has been mentioned that all the patients in the present study were in a pronounced state of vascular or pain shock provoked by the myocardial infarction The patients were clearly suffering from stress which presumably provoked the gastric ulcerations The mechanism of the cause is not quite clear Although nine of the patients were given anticoagulation treatment, this alone cannot be presumed to be responsible for the gastric haemorrhage, though a possible contributory effect cannot be altogether excluded The p p values were not under the lowest therapeutical level at the time when the gastric haemorrhage occurred However, caution should be used in administering heparin subcutaneously, as the bleeding time is never normal and thus there is no possibility of spontaneous arrest of any bleeding in the gastric mucosa

Five of the patients were given antishock treatment with norepinephrine which, as mentioned above (11), could possibly provoke gastrointestinal haemorrhage However, the other eight patients were not given norepinephrine One or two of these patients received pethidine, and as it has been reported (3) that morphine may cause gastrointestinal bleeding the actual sequence of the cause is made even more difficult to elucidate

However, it is important to bear gastrointestinal bleeding in mind as a complication in myocardial infarction It seems to occur in about 1 % of the cases often without any clinical symptoms such as heamatemesis or melaena so that the disease is often not diagnosed until post mortem

Summary

A material is presented consisting of 13 patients with gastric haemorrhage following myocardial infarction with shock due to pain or vascular insufficiency All except two patients died in shock This condition occurs in about 1 % of the total material observed Often no clinical



Fig 1 Appearance of gastric mucosa from a 72 year old female dying in shock from myocardial infarction

of them died two nine and eleven days after the bleeding which was not so massive as to cause death The cause of death must be assumed to be the myocardial infarction itself or the subsequent state of collapse

Table II shows the clinical state of the 11 patients during the period before death and before the haemorrhage in the case of the two surviving patients It will be seen from the table that six patients were suffering from vascular shock which in five of the cases was treated by infusions Patient no 6 died before norepinephrine infusion could be given It must be emphasized here that none of the patients treated with norepinephrine showed any clinical signs of bleeding There is no doubt whatsoever that they were in a state of stress because of vascular shock

All the remaining seven patients had so much pain during the hours before death that they had certainly been exposed to considerable stress

Table III shows the post mortem findings in the gastric mucosa of the 11 patients who died and were examined by autopsy All the ulcerations or mucosal haemorrhages were found to be localized in the gastric mucosa except in case 11 where the pathological findings were most pronounced in the duodenum

Generally numerous more or less extensive superficial haemorrhages or erosions in the mucosa were found There was often free blood in the stomach although only one of the patients (case 1) had clinical bleeding before death

A markedly peculiar gastric mucosa is shown in fig 1, this derives from a 72 year old widow admitted unconscious in shock Two days before admission the patient had consulted a specialist who diagnosed myocardial infarction on the basis of an electrocardiogram The night before admission a violent attack of pain in the cardiac region caused the patient to ring the doctor who called on her several times during the night and gave her injections of morphine In the morning the patient was admitted to the hospital unconscious and in a state of shock and died 55 minutes later without having been given any anticoagulant therapy The post mortem findings revealed numerous flat black spots of the size of peas which gave the gastric mucosa an almost leopard like appearance

Microscopy revealed brownish corpuscles in the uppermost layers of the mucosa which were interpreted by the pathologist (Vesterdal Jorgensen) as being blood which had been under the influence of gastric acid These corpuscles could be seen from the surface to half way down into the mucosal layer where a small fringe of polynuclear leucocytes was found thus indicating that the lesions were intravital in origin Many dilatated small venules were found in the mucosa That microscopical finding must be considered typical since it was seen repeatedly when examining the other gastric layers It is not impossible that the haemorrhage found in the majority of the cases in this study may be due to breakage of such large submucous veins

Discussion

Several theories have been put forward concerning the possible mechanism responsible for acute gastrointestinal ulcerations The first of these is that a con

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Severe Arterial Hypoxemia and Liver-cell Necrosis in Patients with Pulmonary Insufficiency

By

H E Refsum

Recent studies of patients with severe pulmonary insufficiency have shown that the lower limit of arterial oxygen content which for limited periods is compatible both with consciousness and with survival is probably about 6 ml/100 ml blood (25) and that a decrease of the arterial oxygen content to between 9 and 6 ml/100 ml leads to increased activities of cellular enzymes in serum (26) The iso-enzyme pattern of serum lactic dehydrogenase and the liver cell necrosis observed in some of the reported cases indicate that the released enzymes are of hepatic origin and that a close relationship therefore exists between arterial hypoxemia and severe liver cell derangement

It is well established experimentally that severe arterial hypoxemia may lead to liver cell necrosis (1, 5 11 14 29, 27 28) However with regard to the relationship between arterial hypoxemia and liver cell damage in man the liver examinations have usually been made after relatively acute hypoxemia, resulting in death within a short time before development of necrosis the degree and duration of the hypoxemia having not been recorded accurately (5, 7, 21) Both the experimental and the clinical observations have usually been made in cases presenting hypoxemia associated with hypocapnia There seems to be no record of any investigation of the relationship between degree of hypoxemia and liver cell changes in patients with pulmonary insufficiency also suffering from hypercapnia

The purpose of this publication is to report on post mortem liver sections from patients with pulmonary insufficiency, suffering from combined hypercapnia and hypoxemia in whom the arterial oxygen has been lower than 9 ml/100 ml, probably for periods of several hours duration, at varying time intervals before death

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symptoms of gastric haemorrhage, such as *haematemesis or melaena*, are found The possible causes of gastric haemorrhage, following myocardial infarction, are discussed

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Methods

The sampling of arterial blood and the blood gas determinations were performed as described previously (24 25) The arterial oxygen content was calculated from the arterial hemoglobin concentration and the hemoglobin oxygen saturation spectrophotometrically determined

About 2 hours after death the bodies were placed in a refrigerated room, and autopsy was performed within 12—24 hours Material for microscopic examination was fixed in 4% formalin Paraffin sections 5 μ thick were stained with hematoxylin and eosin With the procedure adopted, autolytic changes were moderate and did not affect the microscopic study materially The description of the microscopic picture was performed by Prof K Arnesen, without knowledge of clinical or other data

Results

Table I shows the post mortem microscopic appearance of liver sections from 16 cases with an arterial oxygen content below 9 ml/100 ml blood, the material being arranged according to the time elapsing between blood sampling and death Marked centrilobular necrosis was observed in 2 cases small focal necroses in 4 cases, and both centrilobular necrosis and focal necroses in one case All showed venous congestion, and 12 showed atrophic changes, of a high degree in 4 cases all with focal necroses No case showed evidence of an increase in connective tissue Fig 1 shows the microscopic appearance of the liver section of case 6 with marked centrilobular necrosis

It appears that among the 8 cases who died within 3 days after the blood sampling and the observation of severe hypoxemia 7 *showed necrotic* changes, while among the remaining 8 cases

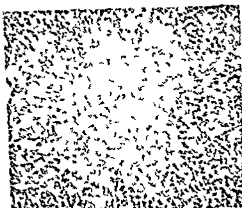


Fig 1 Case 6 Centrilobular necrosis comprising the major part of the lobule (25 7 ×)

with survival of 8 days and more, none showed definite signs of necrosis Among the cases with necrosis the duration of severe failure before start of treatment was about 8 and 12 hours in 2 cases (cases 5 and 6) 24 hours and more in the others Case 1, without signs of necrosis, died 2 hours after the blood sampling less than 8 hours after the start of severe failure

At the time of blood sampling *no* significant difference was observed in the mean arterial oxygen content between the cases with short survival *and necrosis* (7 09 ml/100 ml), and those with prolonged survival and without necrosis (7 23 ml/100 ml) *nor did it appear* that the duration of severe hypoxemia or the severity of the clinical picture was more pronounced in the *former than in* the latter group On the contrary, cases 5 6 and 8, with the severest necrosis, suffering from severe failure for about 12 8 and 24 hours at the time of blood sampling remained conscious until shortly before death, while cases 9, 10 and 16 without necrosis showing severe failure of about the same duration, were

TABLE I Relationship between arterial oxygen content, time between blood sampling and death (in hours or days), and post mortem liver observations in 16 patients with pulmonary insufficiency

Case	Sex	O_2 cont (ml/100 ml)	Survival	Liver weight (g)	Congestion	Atrophy	Necrosis
1	♀	5 8	2 hours	2,000	++	+	–
2	♂	6 9	4 hours	1,350	+++	+++	F
3	♀	7 8	7 hours	1,260	++	+++	F
4	♂	6 4	8 hours	1,940	+++	+++	F
5	♂	6 5	12 hours	1,760	++	–	CF
6	♂	6 1	14 hours	1,720	+	–	C
7	♂	8 3	48 hours	1,190	+++	+++	F
8	♂	7 6	60 hours	1,490	++	++	C
9	♂	8 2	8 days	1,700	++	++	–
10	♂	7 7	9 days	1 500	++	++	–
11	♂	6 1	9 days	1,450	++	++	–
12	♂	6 9	11 days	1,500	+	++	–
13	♀	7 8	17 days	1 290	++	+	–
14	♂	8 4	27 days	1,010	+	–	–
15	♀	6 3	51 days	1,420	++	–	–
16	♂	6 4	108 days	2 350	+++	++	–

+++ = high degree, ++ = moderate degree + = low degree
F = small focal necroses C = centrilobular necrosis

Material

The material consists of 16 patients with severe pulmonary insufficiency due to chronic bronchitis, emphysema, tuberculosis or bronchial cancer At post mortem examination right ventricular hyperthrophy was found in all cases, of marked degree in 12 Right atrial dilatation was observed in 8 cases

The arterial blood sampling was performed during exacerbations of the pulmonary insufficiency, usually at the height of the failure, before treatment The means and ranges of the arterial blood gas values for the cases were Total CO_2 (plasma) 38 1 (29 0—47 0) mEq/l, pH 7 286 (7 16—7 38), pCO_2 79 7 (64—98) mm Hg, HbO_2 39 3 (27 0—50 0) %, pO 25 0 (20—32) mm Hg O_2 cont 7 08 (5 8—8 4) ml/100 ml

The duration of failure at the time of blood sampling was 24 hours or more in 9 cases, 8—24 hours in 6 cases, and less than 6 hours in 1 case (case 1, table I) Death ensued around or beyond 24 hours from the start of exacerbation during which the blood sampling was performed The only exception was case 1 (table I), who died less than 8 hours after the start of the exacerbation and 2 hours after the blood sampling Generally the severe hypoxemia was most probably of several hours duration

Prompted by the blood gas observations, treatment was started with a view to relieving the patients of the hypoxemia and hypercapnia, entailing bronchial suctions, artificial ventilation and oxygen administration Thus from the start of treatment prolonged periods of severe hypoxemia were generally avoided

(case 5), seems to fit the view that the focal necroses may represent earlier and less severe hypoxic lesions than the centrilobular necroses There was no evidence that the focal necroses were associated with prolonged hypotension (8), or with severe bacterial infection, as frequently observed previously (4)

The hepatic circulation is of major importance for the extent of the deleterious effects of arterial hypoxemia Both isolated arterial hypoxemia *per se* (usually accompanied by hypocapnia) and moderate hypercapnia *per se* seem to be associated with reduction of the splanchnic and hepatic blood flow due to increased vasoconstrictor discharge and shifting of the blood to other regions (2, 3 13 16, 18, 23) In what way and how far the hepatic circulation is affected by the combination of severe hypoxemia and hypercapnia, as in the present cases seems unknown (5 29) There is experimental evidence for the possibility that in severe hypercapnia the local effects of carbon dioxide on the vessels can overcome the sympathetic impulses to vasoconstriction, such as predominate in moderate hypercapnia and lead to splanchnic and hepatic vasodilatation and increased blood flow thereby reducing the susceptibility to arterial hypoxemia (5, 6) However, due to the pronounced differences between species with regard to hepatic circulation and to the complex mechanisms for its regulation (5 19) the applicability of experimental observations to more or less chronic pulmonary insufficiency is rather uncertain

The high frequency of liver cell necrosis in the patients with short survival confirms earlier enzymatic observations (26), indicating that an arterial oxygen content below 9 ml/100 ml is usually associated with severe liver cell derangement, but the necrosis need not be centrilobular Whether increased serum enzyme activities may be due to transient alteration of the liver cells and their membrane resulting in the passage of large amounts of enzyme into the blood, without necrosis, seems unknown

Summary

1 Post mortem liver sections have been studied in 16 patients with pulmonary insufficiency, showing arterial oxygen contents between 5 8 and 8 4 ml per 100 ml of blood and carbon dioxide tensions between 64 and 98 mm Hg, probably for several hours at varying intervals before death

2 Among 8 patients who died less than 3 days after the observation of severe hypoxemia 7 showed liver cell necrosis centrilobular or focal, while among 8 patients with a survival of 8 to 108 days during which time severe hypoxemia was avoided as far as possible, none showed definite signs of necrosis

3 The lack of definite signs of necrosis in the patients with prolonged survival is assumed to be due to complete regeneration of the liver tissue in these cases The data seem to indicate that small focal necroses represent less severe hypoxic lesions than centrilobular necrosis The high frequency of necrosis in the patients with short survival confirms earlier enzymatic evidence that an arterial oxygen content below 9 ml per 100 ml of blood is associated with severe liver cell derangement

comatose during the blood sampling Shortly afterwards, one of them (case 16) was subject to *cardiac and respiratory* standstill of several minutes' duration, resulting in persistent mental derangement The therapeutic approach was probably of major importance for the *difference in time of survival*

During the terminal period, there was no difference in body temperature and clinical signs of infection, between those with short and those with prolonged survival Among the cases with necrosis only 2 showed a temperature above 37 6° C, the highest being 38 5° C At post mortem examination 2 showed moderate bronchopneumonic foci (cases 3 and 6), while none showed other signs of severe infection The degree of venous congestion, as evaluated from the clinical picture, the liver weight and the microscopic appearance of the liver sections (table I) was about the same in both groups, and there was no difference with regard to pulse and blood pressure Owing to artificial ventilation and oxygen administration, the cases with prolonged survival were not subject to the same degree of hypoxemia during the last days before death as they were at the time of blood sampling

Discussion

It is well established that complete restitution of the liver parenchyma may take place in the course of 1—2 weeks after extensive *necrosis* (4, 9, 22, 28) Accordingly, there being no evidence that the deleterious effects of hypoxemia at the time of blood sampling, before treatment, were more severe in the cases with short than in those with prolonged survival, the most probable explanation of the differences with regard to necrosis seems to be the following At the time of blood sampling, about the same degree of necrosis may have been present in both groups, but at the time of death complete repair had taken place in those with prolonged survival, during which period severe hypoxemia as far as possible had been avoided The lack of necrosis in case 1, however, may be explained by too short a duration of severe hypoxemia to result in cell death, or, if a lethal hypoxia was present, by too short an interval between death of the liver cells and death of the patient for the development of the cellular changes representative of necrosis, these usually taking several hours (1, 9, 10, 12, 15)

Centrilobular necrosis is regarded as the typical hypoxic liver cell lesion (5, 12, 17) Recent observations indicate, however, that the central parts are not necessarily more susceptible to hypoxia than the peripheral ones (5) Focal necroses may be associated with less severe liver hypoxia than centrilobular necrosis For the smallest focal necroses, sometimes restricted to single cells (1), the cause may be less severe arterial hypoxemia, or less severe and more localized reductions of the hepatic lobular perfusion (1, 8) The presence of marked atrophic changes in the cases with small focal necroses indicates that the cells had been subject to severe derangement, although not severe enough to cause centrilobular necrosis This, together with the fact that the case with moderate centrilobular necrosis, not extending to the major part of the lobule, also showed focal necroses

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Summary

1. Post mortem liver sections have been studied in 16 patients with pulmonary insufficiency, showing arterial oxygen contents between 5.8 and 8.4 ml per 100 ml of blood and carbon dioxide tensions between 64 and 98 mm Hg, probably for several hours, at varying intervals before death.
2. Among 8 patients who died less than 3 days after the observation of severe hypoxemia, 7 showed liver cell necrosis centrilobular or focal while among 8 patients with a survival of 8 to 108 days, during which time severe hypoxemia was avoided as far as possible none showed definite signs of necrosis.
3. The lack of definite signs of necrosis in the patients with prolonged survival is assumed to be due to complete regeneration of the liver tissue in these cases. The data seem to indicate that small focal necroses represent less severe hypoxic lesions than centrilobular necrosis. The high frequency of necrosis in the patients with short survival confirms earlier enzymatic evidence that an arterial oxygen content below 9 ml per 100 ml of blood is associated with severe liver cell derangement.

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The Heart in Myotonic Disease

By

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Myotonia i e abnormal continuation of the contraction of voluntary muscles is a symptom which is present in *myotonia congenita* (M C) and *dystrophia myotonica* (D M), two hereditary disorders This symptom is the predominant feature in M C, whereas in D M a systemic disease, it is only part of a variety of other abnormalities the most outstanding of which is dystrophic muscular disease

Involvement of the heart in D M has frequently been reported by various authors (5 8 11 13 15 17 19, 21 25, 26 27 36) In a recent monograph on myotonic disease Pipberger (18) summarized most of the pertinent literature and critically integrated the findings of numerous investigations Signs which have been attributed to cardiac alterations in D M are low blood pressure, bradycardia arrhythmias and delayed atrioventricular and intraventricular conduction In general three theories have been proposed for the pathogenesis of these changes 1) *hyperactivity of the vagus* (6) 2) *arteriosclerotic heart disease* (29) 3) *dystrophic myocardial disease* (7 9 21)

M C on the other hand seems not to be connected with an unusually high rate of heart disease There are however only two reports of a few cases containing information as to cardiac investigation in this disease (23 27)

It is the purpose of this study to give a more detailed description of cardiac alterations in a comparative study of cases of M C and D M in order to clarify the nature of these abnormalities In most cases follow up studies of many years have been performed Moreover, the result of exercise test, and vectorcardiography will be presented as well as detailed postmortem study with histological examination of the heart

Material and methods

This study is based on 6 patients with M C (ages 17—81) and 29 patients with D M (ages 24—62) There were 2 *women in the* group with M C and 9 in the group *with* D M (table I) All patients exhibited both active and mechanical myotonia All M C patients and 27 D M patients have been

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TABLE I Summary of cardiovascular changes (myotonia congenita 1-6 dystrophia myotonica 7 35)

Clinical findings							Electrocardiography			
Case no	Sex, Age (yrs)	Duration symptoms (yrs)	Functional capacity	Heart rate	B P (mm Hg)	Heart vol (ml/m^2)	P R (sec)	Q S (sec)	Other changes	Result of follow up
1	♂ 81	Cong	I	80	190/110	450	0 17	0 08	—	4 yrs unchanged
2	♂ 53	Cong	I	85	125/75	400	0 17	0 09	—	—
3	♀ 52	Cong	I	80	145/95	Normal	0 17	0 07	—	2 yrs unchanged
4	♀ 45	Cong	I	65	135/85	390	0 16	0 08	—	—
5	♂ 17	Cong	I	60	110/70	240	0 16	0 08	—	—
6	♂ 33	Cong	I	65	115/85	390	0 14	0 08	—	1 yr, unchanged
7	♂ 50	11	I	70	115/95	Normal	0 18	0 10	—	5 yrs QS 0 09—0 10
8	♂ 40	9	I	70	120/90	330	0 17	0 08	—	5 yrs unchanged
9	♀ 53	24	III	70	110/85	280	0 22	0 10	Slurred QRS	19 yrs, PR 0 17—0 22 QS 0 08—0 10
10	♂ 40	12	I	70	115/85	410	0 21	0 10	—	4 yrs PR 0 17—0 21 QS 0 08—0 10
11	♂ 50	23	III	70	125/95	300	0 22	0 13	Abn Q ant cond defect	2 yrs QS 0 11—0 13
12	♂ 34	12	II	80	135/85	370	0 20	0 10	—	4 yrs, QS 0 08 —0 10
13	♂ 45	15	III	60	130/70	380	0 20	0 10	Slurred QRS	7 yrs, QS 0 08 —0 10
14	♂ 24	10	II	85	135/85	320	0 18	0 09	Slurred QRS	—
15	♂ 57	8	II	70	165/105	350	0 28	0 09	—	5 yrs unchanged
16	♀ 28	10	II	50	100/60	300	0 18	0 10	—	3 yrs QS 0 08—0 10
17	♂ 54	25	II	90	125/70	520	—	0 17	Aur flutter	
				60	100/80	440	0 21	0 17	Cond defect sinus rhythm	2 yrs, QS 0 15—0 17
18	♂ 38	10	I	60	120/80	Normal	0 21	0 11	Aur fibr sinus rhythm	—
19	♀ 42	15	II	95	145/85	260	0 18	0 10	Slurred QRS	—
20	♂ 61	12	II	45	105/75	390	0 19	0 10	Slurred QRS	10 yrs QS 0 08—0 10
21	♀ 42	7	II	55	125/85	390	0 20	0 10	Slurred QRS	—
22	♂ 53	12	II	60	125/70	480	—	0 16	Aur fibr cond defect	6 yrs QS 0 13—0 16
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24	♂ 61	12	II	70	155/65	390	0 19	0 13	Cond defect	11 yrs altered conduction

TABLE 1 (cont)

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26	♂ 34	7	I	50	110/85	330	0 21	0 10	Slurred QRS	—
27	♀ 40	16	II	80	125/95	Normal	0 18	0 07		4 yrs unchanged
28	♂ 41	16	II	70	125/80	680	—	0 10	Aur fibr slurred QRS	1 yr QS 0 09—0 10
29	♀ 41	20	II	65	110/70	290	0 20	0 09	—	—
30	♂ 39	Unknown	III	120	130/80	—	0 17	0 09	—	—
31	♂ 34	13	II	80	140/100	—	0 19	0 09	—	—
32	♂ 62	34	III	110	125/90		—	0 10	Aur fibr slurred QRS	26 yrs sinus aur fibr QS 0 07—0 10
33	♂ 33	1	I	65	140/90	320	0 18	0 08	—	—
34	♀ 56	11	I	65	160/80	360	0 18	0 08	—	1 yr unchang d
35	♀ 34	8	I	70	140/75	250	0 17	0 08	—	3 yrs unchang d

investigated with electromyography and all showed specific electrical activity Five of the cases with M C belong to the same family representing 3 generations (cases 1—5) In addition to myotonia all patients with D M exhibited other characteristic features such as muscular atrophy and weakness mental deterioration cataracts as well as premature baldness and testicular atrophy in men Many of these patients had a positive family history of D M

Assessment of functional capacity I order to elucidate the severity of the disabling symptoms in the D M patients we have adopted an arbitrary grading according to the functional state of the patient Grade I includes 8 patients who were able to maintain some gainful work Grade II comprises 15 patients who were unable to work but who were able to take care of their personal hygiene Grade III patients were bedridden or unable to perform any kind of useful physical or mental activity (6 cases)

Electrocardiograms were recorded in all patients with a four channel direct writing electrocardiograph Standard limb leads I II and III augmented unipolar leads aVR aVL and aVF and 5 precordial R leads were taken

Vectorcardiograms were obtained according to the Grishman cube technique of electrode placement (10) and recorded with a Sanborn vectorcardiograph Projections of the spatial vectorcardiograms on the frontal right sagittal and horizontal planes were recorded separately The vector loop was interrupted every 2 5 msec for accurate timing In order to determine the direction of the rotating

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29	♀41	20	II	65	110/70	290	0 20	0 09	—	—
30	♂39	Unknown	III	120	130/80		0 17	0 09	—	—
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32	♂62	34	III	110	125/90		—	0 10	Aur fibr slurred QRS	26 yrs sinus aur fibr QS 0 07—0 10
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TABLE II Pathological evaluation of the heart

Case no	Sex, Age (yrs)	Cause of death	Heart weight (g)	Myocardial fibre diameter (Mean±SD) (μ)	Atherosclerotic vessel changes[1]	Comments
Myotonia congenita						
1	♂ 81	Encephalomalacia Ulcus perforans duodeni	515	13 8±3 0	II—III	Moderate perivascular and interstitial fibrosis with some fibre degeneration No lipomatosis
Dystrophia miotonica						
9	♀ 53	Broncho-pneumonia	360	12 5±2 7	I	Slight perivascular and very slight interstitial fibrosis No lipomatosis
23	♀ 47	Broncho pneumonia	190	14 3±2 6	I	Slight perivascular and very slight interstitial fibrosis No lipomatosis
30	♂ 39	Broncho-pneumonia	300	12 8±2 2	II	Moderate perivascular and slight interstitial fibrosis No lipomatosis
32	♂ 62	Broncho-pneumonia	320	12 7±2 5	II—III	Extensive perivascular and moderate interstitial fibrosis with some fibre degeneration. Slight lipomatosis
Normal hearts						
	♀ 23	Glioblastoma	270	13 3±2 5	0	Very slight perivascular and interstitial fibrosis No lipomatosis
	♀ 21	Glioblastoma	300	13 3±2 5	0	Very slight perivascular and interstitial fibrosis No lipomatosis
Hypertensive heart						
	♂ 60	Haemorrhagia cerebri	700	21 2±3 3	II—III	Moderate perivascular and interstitial fibrosis with some fibre degeneration Slight lipomatosis

[1] Arbitrary grading of changes in coronary arteries and myocardial vessels 0 — no changes
I = slight
II = moderate
III = extensive

loop the interrupted lines are wedge shaped with the wider end leading

Exercise tests were performed with a bicycle ergometer designed by Holmgren and Mattsson (12) Electrocardiograms (chest leads) were recorded simultaneously during exercise, immediately after and 4 and 10 min after cessation of work The heart rate and respiratory frequency were determined every 2 min at increasing work loads according to Sjöstrand (24) and Wahlund (28) In a few instances ECGs were recorded while the patients breathed a low oxygen mixture

Chest X ray examinations with determination of the cardiac volume in ml/sq m of body surface area were performed in 32 cases

Pathological examinations During the observation time seven patients died Autopsy findings were recorded from five of these Complete anatomical and histological investigations were thus performed in one case of M C (case 1) and in 4 cases of D M (cases 9 23 30 32) In order to make a comparative analysis of the histological data the hearts from two young women (aged 21 and 23) who died as the consequence of malignant brain tumours and who had no evidence of cardiac disease were examined Moreover a histological examination of the heart of a case with arterial hypertension and cardiac hypertrophy was obtained The microscopical study included examination of the coronary arteries with their branches and intramural extensions as well as an investigation of myocardial fibres and interstitial tissue from different parts of the heart In order to be able to make a quantitative comparative analysis of the diameter of myocardial fibres from different hearts we have measured fibre diameters with the aid of a microscopic ocular micrometer (Carl Zeiss) at a magnification of 400 × The measurements were performed only in myocardial fibres with a transverse section For this purpose those fibres were chosen whose sections displayed a regular circular or slightly oval delineation Comparative measurements from different parts of the cardiac musculature (Sinospiralis sup and prof as well as Bulbospiralis sup) performed in cases with D M with M C with a normal heart and with a hypertrophic heart showed a uniform distribution of fibre diameters from different parts of the heart the data given in table II are therefore derived only from measurements of the sinospiral muscles which can be considered to be representative of the entire heart In each case 100 determinations of fibre diameters have been made The results of these measurements given in table II are the arithmetic mean and one standard deviation

Results

Clinical findings (A summary of the clinical findings is given in table I) In the present series there was only one case (no 28 D M) with cardiac failure, exhibiting moderate symptoms of dyspnoea on exertion, auricular fibrillation and cardiac enlargement Four other cases of D M had slight dyspnoea on exertion (nos 9, 14, 17 and 29) Angina pectoris was not present in any case In only three cases was a slight systolic murmur noted Moderate hypotonia was present in three cases of D M (nos 16 17 and 20) The lowest blood pressure in this category was 100/60 mm Hg Otherwise blood pressure was normal with the exception of one case of arterial hypertension in the group of patients with M C (no 1) In this case the blood pressure was 190/110 mm Hg The highest blood pressure in the group of D M found in only one case was 165/105 In this one patient a previous reading was 160/90 and later a value of 125/95 mm Hg was recorded

X ray examination of the chest revealed enlargement of the heart of a moderate degree in 3 cases of D M with values of 480 520 and 680 ml/sq m of body surface area (table I)

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TABLE III Result of exercise tests Heart rates at increasing work loads (kpm/min) Single values after a period of 2 min only are indicated by Italics

Case no	Sex Age	200	300	400	600	900	1 200	Remarks
1	♂ 77	—	120	—				Advanced age
5	♂ 17		100		135	170	—	
6	♂ 32	—	105		140	175		
7	♀ 45		105		155	165		
8	♀ 35		110		140	*165*		
10	♂ 40		115		120	145	175	
12	♂ 34		150		160			—
13	♂ 49		135					Muscular weakness
15	♂ 52		115		135	*155*		
16	♀ 25	85		110	*140*			
17	♂ 52		*175*					Auricular flutter
20	♂ 61		110		*130*			Muscular weakness
24	♀ 59		*120*		*135*			Muscular weakness
25	♂ 43		90		115	*140*		
26	♂ 34		90		120	150	170	
28	♀ 41	140		*170*				Auricular fibrillation
29	49	110		135	*160*			
33	♀ 33		110		145	170	*180*	
34	56	*1 ?*						Muscular weakness
35	24	120		140	60			

varying degrees of ST and T wave deformities but these changes seemed to be secondary to the intraventricular conduction defect

Q T intervals were slightly increased in five cases four cases of D M and one of M C

Exercise tolerance tests were performed in 20 cases The electrocardiographic response was normal throughout including two cases in which a hypoxia test was performed

The heart rate values during exercise determined electrocardiographically are listed in table III These figures may serve as a rough estimate of the patients physical working capacity which will be discussed later In only one case no 12 it was slightly low All the other patients had apparently a normal heart rate response on graded muscular work

The vectorcardographic tracings revealed intraventricular conduction defects of varying degrees (fig 2) Note the proximity of the interrupted time markings indicating delay of intraventricular conduction All cases presented conduction delay of the terminal portion of the loop Moreover this was oriented superiorly from the point of origin In addition delayed conduction could be traced back to the middle part of the loop in all cases In 3 cases nos 17 22 and 24) an initial conduction delay could also be encountered The major portions of the QRS loop were inscribed in a reversed direction

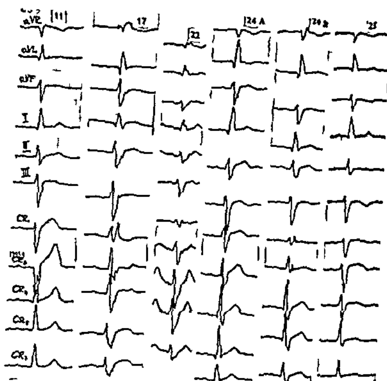


Fig 1 Some typical electro cardiograms from patients with dystrophia myotonica (cases nos 11 17 22 24 and 25 cf the tables)

Electrocardiographic findings (table I) There were no electrocardiographic ab normalities in the category of M C Normal electrocardiograms in patients with D M were present in only 11 cases out of 29 (38 %) Slow heart rate was not a very common finding *Bradycardia* with heart rates below 50/min was present in four cases of D M

Auricular fibrillation was present in 5 cases and auricular flutter in one *Prolonged AV conduction* time (exceeding 0 20 sec) was noted in 8 cases (28 %) with a maximal value of 0 28 sec There were 4 borderline cases with a PR interval of 0 20 sec *Prolonged intraventricular conduction time* (above 0 10 sec) was present in 7 cases with values up to 0 17 sec In another 12 cases intervals of 0 10 sec were found If these cases are included, then varying degrees of intraventricular conduction defects were present in nearly 70 per cent of the cases of D M

The intraventricular conduction defects were difficult to classify electrocardiographically There was no case which fulfilled the electrocardiographic criteria of typical bundle branch block Most cases showed features characteristic of both left and right ventricular conduction delay and left axis deviation The tracings of some typical cases are shown in fig 1 The electrocardiograms of case nos 11 and 23 present abnormal Q waves Duration and amplitude of these deflections were highly suspicious of myocardial damage according to conventional criteria With the exception of one case (no 28) there were no signs of disturbed repolarisation (ST and T wave changes) Those cases with marked intraventricular conduction defects however presented

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8	♀ 35	—	110	—	140	*165*	—	—
10	♀ 40	—	115		*120*	145	175	—
12	♀ 34	—	150		160		—	—
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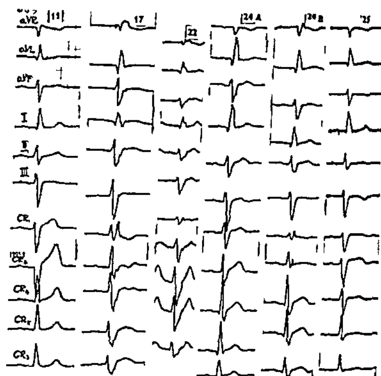


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in the frontal plane in all but one case (no 17) with ordinary sense of rotation in the sagittal and horizontal planes The vector loops of case nos 17 and 22 presented some peculiar irregularities with distortion of the entire QRS loop The T loops were essentially discordant to the maximal QRS-vector In our cases the vectorcardiograms revealed no resemblance to those characteristic of left or right bundle branch block

Follow-up studies Twenty three cases have been investigated repeatedly during the observation time, which ranged from 1 to 26 years As evident from table I in most D M cases a slowly progressive increase in atrioventricular and intraventricular conduction times was noted In one D M case (no 24) a marked change in the pattern of intraventricular conduction defect could be disclosed by serial electrocardiographic tracings (fig 1, 24 A and B)

Pathological examination Autopsy findings are listed in table II In none of the cases was there any evidence suggesting valvular disease or gross anatomical alterations of the myocardium such as infarction or myocarditis The degree of atherosclerotic vessel changes present in the coronary arteries or their intramural branches did not show any difference as compared with the picture usually encountered in other cases of the same sex and age

As evident from the figures in table II there is no significant difference between fibre diameters in patients with M C, with D M and with the control cases The size and contour of the nuclei of myocardial fibres varied with fibre thickness The observed degree of perivascular and interstitial (mainly perimysial) fibrosis seemed to be well correlated to the degree of arteriosclerosis present in the coronary arteries Myocardial fibrosis therefore, does not seem to be a characteristic feature of D M The type of myocardial fibrosis present in all cases seemed to be of a uniform nature Interstitial lipomatosis and muscular pigmentation were found to be insignificant in patients as well as in controls

Discussion

There was a striking difference between the very frequently encountered electrocardiographic alterations and the incidence of clinical heart disease in D M This is evident from the few cases with evidence of *congestive heart failure* Judging from the literature an overall incidence of about 7 per cent of heart failure could be found to exist in a total series of 195 cases collected from the literature (7, 8, 13 14, 15 16 21 23 25 30) In our series of 29 cases of D M there was only one case with a moderate degree of cardiac insufficiency (no 28)

Electrocardiography A review of the literature reveals that the incidence of electrocardiographic abnormalities is high in patients with D M According to Fisch s (8) comprehensive series collected from the literature, abnormal tracings could be found in 68 per cent of 85 patients studied electrocardiographically In our series there was the same incidence of abnormal electrocardiograms (18 out of 29 cases of D M) In this series however, delayed intraventricular conduction was more frequently encountered than pro-

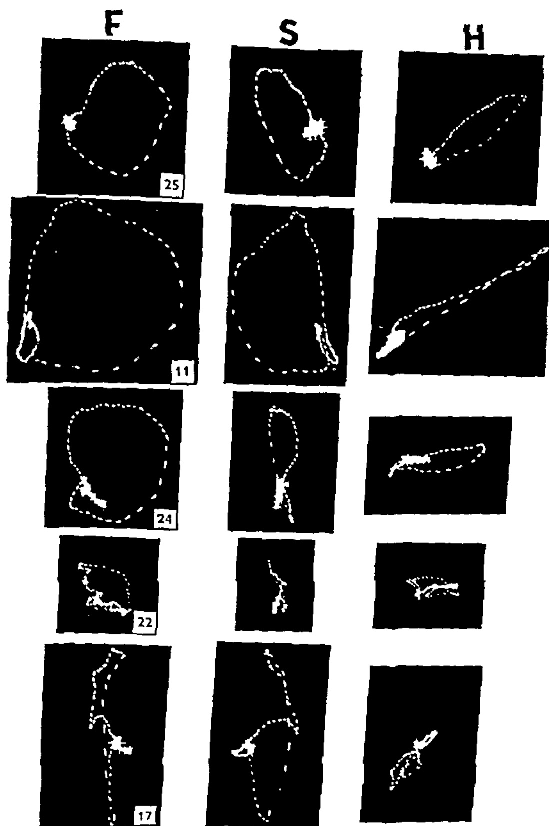


Fig 2 Vectorcardiograms from patients with dystrophia myotonica and intraventricular conduction defects (cases nos 11 17 22 24 and 25 of the tables

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Electrocardiography A review of the literature reveals that the incidence of electrocardiographic abnormalities is high in patients with D M According to Fisch s (8) comprehensive series collected from the literature abnormal tracings could be found in 68 per cent of 80 patients studied electrocardiographically In our series there was the same incidence of abnormal electrocardiograms (18 out of 29 cases of D M) In this series, however, delayed intraventricular conduction was more frequently encountered than pro-

longed PR-intervals which was the predominant alteration in Fisch's series Our follow-up studies showed that the development of electrocardiographic alterations occurred slowly over a long period of time Kuhn (15) made the same observation

Vectorcardiography Intraventricular conduction disturbances are recognized by slowing of the rate of inscription of the QRS-loop This is evident by the proximity of the time markings Moreover, there is distortion and irregularity of the loop In bundle branch block some characteristic features can be recognized The slowing usually occurs in a specific portion of the loop while other sections are inscribed at a normal rate In right bundle branch block the terminal portion of the QRS-loop shows slowing and usually some typical deformations which can be described as a "terminal appendage" This is essentially oriented anteriorly to the right Moreover, in right bundle branch block *the QRS loops* are usually inscribed in the normal rotation in each plane *The most significant alteration of* the QRS-loop in left bundle branch block is delayed conduction *in the middle* portions without formation of a terminal appendage The sense of rotation is reversed in the horizontal plane so that the QRS loop is inscribed in a clockwise direction Moreover, in left bundle branch block the QRS vectors are predominantly oriented in a posterior and leftward direction (10)

Our D M cases with intraventricular conduction defects do not exhibit features which fit this description *In all cases both* a terminal and more central part of the loop presented signs of conduction delay Thus vectorcardiographic and electrocardiographic patterns in our patients were different from those found in bundle branch block according to conventional criteria

One case showed suggestive vector cardiographical features of anterior myocardial infarction (no 11), and two other cases (nos 24 and 25) showed some features suggestive of unilateral ventricular hypertrophy These findings, however, could not be corroborated by clinical findings This also applies to case no 23 with abnormal Q waves in the electrocardiograms In this case no localized myocardial damage could be disclosed at autopsy and, moreover, the coronary vessels were normal

When comparing the patients' *functional capacity* and the duration of symptoms as listed in table I, it is evident that there is a rough correlation between the length of the illness and the degree of *disablement* in patients with D M Those patients who had *D M for more than* 15 years exhibited a variety of symptoms severel *interfering* with *ordinary* physical and mental activity A similar correlation however, cannot be shown to exist when considering the degree of electrocardiographic abnormalities, as illustrated by the incidence of prolonged intraventricular conduction time, the most frequently occurring alteration among the D M patients

The heart rate during the exercise *tolerance* tests, as evident from table II can be discussed from the *viewpoint of* estimating the patient's *physical working capacity and the fitness of his* circulatory system The heart rate during muscular work is highly correlated with the degree of ex-

ercise performed, rising linearly with increasing work loads Furthermore there is a correlation between heart rate values at steady state and the individual s oxygen uptake This has been demonstrated in studies by Sjostrand (24) and by Åstrand (2) Thus heart rate values at "submaximal work loads may serve as a rough guide of a patient s physical fitness In the present series the majority of cases had a normal physical working capacity as judged from the heart rate values The limiting factor determining physical fitness in most cases was weakness of skeletal muscles and not decreased circulatory function

The pathogenesis of the cardiac alteration in D M is still obscure We are of the opinion that the myotonic phenomena can be ruled out as the causative factor This is supported by the comparison of the cases with M C and D M both of which have myotonia in common but electrocardiographic changes are present only in D M Other evidence against the assumption that the heart participates in myotonic contractions has been presented by Segura and Lanari (22) and Bartley and Örndahl (3) The latter two authors came to this conclusion in a study with electrokymography

Dysfunction of the autonomic nervous system with hyperactivity of the vagus seems to be unlikely in view of the predominance of intraventricular conduction defects in our series Slowing of the heart rate and the delayed atrio-ventricular conduction may be mediated by cardiac parasympathetic nerve supply but intraventricular conduction delay of the kind reported here is unlikely to be related to hyperactivity of the vagus

It has been suggested that coronary sclerosis might be responsible for the observed cardiac alterations (29) The results of exercise tolerance tests performed in this study, however present no evidence in favour of coronary insufficiency and moreover, the observed vessel changes of the autopsied cases were by no means remarkable but they seemed to correspond to the type of changes ordinarily found in these age groups

It seemed important to perform a detailed anatomical investigation of the heart in patients with D M in order to clarify whether the observed electrocardiographic changes can be considered to be a sign of generalized dystrophic muscular disease also affecting the myocardium Therefore, it was of interest to see whether such changes could be found also in cardiac muscle In order to get a quantitative assessment of dystrophic muscular changes we performed an analysis of myocardial fibre diameters in cases with myotonic disease and in controls The results of this study (cf table II) do not support the view that myocardial dystrophy is of any importance in the present series of patients since both patients and controls showed the same distribution of fibre diameters

Roberts and Waern (20) determined diameters of myocardial fibres in 26 cases (aged 25—77) who did not present evidence of heart disease These authors found mean fibre diameters of 13 9 $\pm$ 0 2 μ (mean $\pm$ S E of mean) They concluded that arteriosclerotic vessel changes did not affect fibre diameters a finding which is in accordance with our experience On the other hand, these authors were of the opinion that there was

a direct correlation between fibre diameter and heart weight We could not establish such a correlation for our M C and D M cases, however, The cross sectional fibre size of our controls (two normal hearts and one hypertrophic heart) shows values which fit the fibre size to heart-weight relationship proposed by Roberts and Wearn In cases with progressive muscular dystrophy cardiac changes of dystrophic type have been reported to be common by Berenbaum and Horowitz (4) Descriptions of pathological findings in hearts from D M patients (eg 5, 9, 21) have demonstrated diffuse myocardial fibrosis most certainly related to coronary sclerosis, but not fulfilling the criteria of dystrophic muscular involvement

The moderate atherosclerotic vessel changes in the coronary arteries cannot account for the high incidence of conduction abnormalities noted in D M patients Because of the diffuse type of the intraventricular conduction defects encountered in these patients, focal damage of the cardiac conduction system is unlikely, whereas diffuse changes within the bundle branches and the Purkinje network may be a more adequate explanation

Summary

Clinical, electrocardiographic, vectorcardiographic and histological observations from 29 cases of dystrophia myotonica are reported In addition a comparative analysis of 6 cases of myotonia congenita is presented

The following general conclusions may be made

The cardiac alterations observed in dystrophia myotonica seem to be of minor importance with respect to circulatory function and ultimate prognosis

Clinical signs of heart disease with cardiac failure were present in only one case, the predominant feature being electrocardiographic abnormalities (62 per cent) Among these, intraventricular conduction defects of varying degree prevailed The vector- and electrocardiographic findings show intraventricular conduction defects which seem to be indicative of diffuse changes of the specialized cardiac conduction system rather than the contractile elements of the myocardium

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Weakness of Proximal Limb Muscles, Probably Due to Myopathy after Partial Gastrectomy

Preliminary Report

By

K Ekbom, R Hed L Kirstein and K E Åström

In recent years increasing interest has been paid to sequelae of partial gastrectomy such as the malabsorption syndrome (5 11)

However disturbances in muscular functions have, to the best of our knowledge not been studied previously

This preliminary report deals with three patients in whom a *proximal* muscular weakness developed after Billroth II resections for gastroduodenal ulcers Electromyography demonstrated signs of myopathy but definite histological abnormalities were lacking Evidence of malabsorption could be found in all cases and improvement of the muscular strength followed in two of them after administration of vitamin D in large doses

Case reports

Case 1 A 61 year old man underwent a Billroth II partial gastrectomy in 1950 because of a gastric ulcer Ever since the operation he had suffered from anorexia and had lost weight His diet had been low in milk and cheese

In 1955 he noted a weakness of the legs particularly when climbing stairs or when entering a tram (street-car) and the symptoms slowly progressed during the following year There were no sensory complaints

On physical examination in 1956 the patient appeared remarkably thin There was pronounced weakness and atrophy of the proximal limb and girdle muscles of all extremities He was unable to step up on a chair or get up from a squatting position He had difficulty in raising his head from a supine position Deep tendon reflexes were active and equal and the plantar responses were flexor There were no fasciculation Sensibility and the cranial nerves were normal

Electromyography On examination of the left sternomastoid muscle very marked polyphasic potentials with a duration less than 5 msecs were seen on voluntary contraction i e a pattern typical of myopathy

A biopsy from the right glutaeus maximus muscle revealed degeneration of single fibers a slight infiltration of fat cells and a moderate generalized atrophy of the muscle fibers A biopsy from the left quadriceps muscle was almost normal

Radiography demonstrated a moderate to high grade decalcification in the bones and a questionable Milkman s fracture in the lower part of the right femur

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TABLE I Laboratory data in 3 gastrectomized patients with proximal muscle weakness and malabsorption syndrome The peroral intake of calcium was between 1 000 and 1,700 mg daily

Case	Blood Ca (mg%)	Blood P (mg%)	Alkaline phosphatase (Buch & Buch units)	Urinary excretion of Ca (mg/24 hrs)	Fecal fat content (g/24 hrs)
1	8 5	2 8	8 6	39	10 7
2	7 6	2 8	31 0	5	10 0
3	10 2	2 6	10 4	18	18 2
Normal	9 0–11 0	2 5–5 0	2–7	—	<6

Relevant laboratory data are given in table I

The patient did not attend control examinations and treatment with vitamin D was not tried

Case 2 A 48 year old man had had periods of hypochromic anemia, diarrhea and loss of weight for 20 years In 1952 at the age of 41, a Billroth II partial gastrectomy was performed because of a gastric ulcer with pyloric stenosis In 1954, following a period of frequent diarrhea and weight loss, his arms and legs became progressively weaker He had difficulty in climbing stairs and eventually became unable to walk without the aid of two canes He was bedridden during the last 2 months before admission Except for occasional numbness of his feet there had been no sensory symptoms

Physical examination on admission in 1958 revealed a pale, ill nourished male He was weak generally but the muscle strength was reduced especially proximally in the limbs He was unable to rise from a supine position or to get up from a chair and he could not elevate his legs more than a few centimeters from the bed He had to be supported when standing and the gait was greatly impaired

The muscle mass was generally reduced but there were no localized atrophies and no fasciculations The deep tendon reflexes were present The cranial nerves and the sensation were unimpaired

Electromyography was performed on the left quadriceps muscle Voluntary contraction gave rise to an interference activity In patchily distributed areas the potentials were to a large extent diphasic with a duration of 1 5 to 2 msecs, triphasic up to 3 5 msecs and polyphasic of a duration between 3 and 5 msecs The pattern was thus characteristic of myopathy

A biopsy from the left quadriceps muscle showed an almost normal appearance

Radiography displayed a diffuse moderate decalcification in the skeleton

Relevant laboratory data are given in table I Metabolic balance studies were performed (fig 1)

After treatment with vitamin D the calcium balance rapidly became positive The muscle strength was greatly improved and the patient was able to walk without support

Recovery was complete, and after 5 years on a daily dose of 26,000 I U vitamin D the patient is still free from symptoms and able to work

Case 3 A 50 year old woman had undergone a partial gastrectomy according to Billroth II in 1954 because of a duodenal ulcer Except for moderate postcibal symptoms she was well until the early part of 1962 when she noticed dyspnea at exertion frequent loose, foul smelling stools and a gradually progressing weakness of the limbs She had difficulty in climbing stairs and lifting heavy objects

On admission in Dec 1962 there was a slight weakness in the shoulders and a marked weakness proximally in the lower limbs She was unable to rise from a sitting or squatting position or to step up on a chair Both quadriceps muscles showed moderate atrophy There were no fasciculations The deep tendon reflexes were present and no pathologic reflexes could be elicited The sensation and the cranial nerves were normal

Electromyography The voluntary activity was recorded from the right quadriceps muscle On maximal voluntary contraction there was an interference pattern In 25 potentials the mean potential duration was 5 0 msecs This low value is consistent with myopathy

A biopsy from the right quadriceps muscle was normal except for a slight infiltration of fat cells

X ray examinations disclosed a moderate to pronounced decalcification of the skeleton

Laboratory data are given in table I

Following the administration of 70 000 I U of vitamin D daily the alkaline phosphatase level increased slightly and the patient complained of a moderate diffuse aching of her back for 1—2 weeks Then the weakness decreased gradually and she was able to rise from chairs and climb stairs more easily

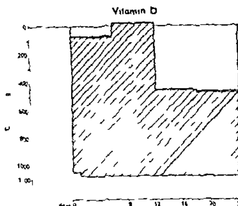


Fig 1 Metabolic study in case 2 Peroral intake of calcium 1 060 mg daily Before treatment the feces yielded amounts of calcium dose to that ingested After peroral treatment with vitamin D 250 000 I U daily the patient retained about 450 mg of calcium per day and was in a strongly positive calcium balance Note very low urinary calcium excretion throughout.

urine ▨ feces

Discussion

The three patients showed a similar clinical picture Weakness occurred in girdle and proximal limb muscles several years after gastric surgery, the symptoms progressed slowly to complete incapacitation

The proximal muscular weakness the preserved reflexes and sensibility together with absence of fasciculations suggested a myogenic origin of the pareses Electromyography also indicated myopathy in these cases although well-defined histologic alterations were lacking Similarly there is frequently a discrepancy between the muscle weakness and the usually mild or non existing histopathologic changes in myopathies of metabolic or endocrine origin, e g hypothyroidism (17) Cushing s disease (14) and thyrotoxicosis (10)

In our cases there were no evidences of any primary muscle disease or of any other metabolic or endocrine disorders which can give muscular symptoms We have therefore assumed that this muscular syndrome represents a hitherto disregarded complication after gastrectomy although admittedly one patient (case 2) had had periods of diarrhea and weight loss even before the operation Even in this case however, muscular weakness did not appear until after the operation

Malabsorption could be demonstrated in all three cases, and has been studied after gastrectomy elsewhere in the literature during recent years (5, 11)

It is also known that signs of osteomalacia may appear after partial gastrectomy (2, 4, 8, 9, 12, 15), as was suggested by Ask-Upmark in *1939 (1)* His description of a case of his own is instructive a pronounced osteomalacia occurred in a 38-year-old woman some years after a subtotal gastrectomy for ulcer Complete recovery followed upon administration of vitamin D (3)

The presence of osteomalacia is of interest since this condition can be associated with a weakness in proximal muscles, which can regress, sometimes completely, after treatment with vitamin D (7, 13, 16) Sometimes the *muscular weakness can appear before any other manifestation of osteomalacia (6)*

In the present study decalcification of the skeleton was demonstrable *radiographically in all three* patients, but there were no definite signs of osteomalacia However, the laboratory data (hypocalcemia, hypocalcuria increase of serum alkaline-phosphatase level) and the strongly positive calcium balance after administration of vitamin D in case 2 suggested a chemical osteomalacia

A more comprehensive *study* on the occurrence of muscular weakness and malabsorption after partial gastrectomy has now been undertaken by the present authors

Summary

A progressive weakness in girdle and proximal limb muscles occurred in three patients, 2—8 years after partial gastrectomy *for ulcer* Muscle biopsies were almost normal, but the clinical picture and the electromyographical examinations suggested myopathy All patients had also signs of a malabsorption syndrome The pareses decreased in two patients given treatment with vitamin D

The muscular weakness is considered to represent a hitherto disregarded sequel of partial gastrectomy

Acknowledgement

This investigation was supported by a grant from the Swedish Medical Research Council

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Haemorrhagic Diathesis and Anaemia in Scurvy

Report on Three Cases

By

H CH HART J F PLOEM, J T PANDERS and M C VERLOOP

Adults showing the complete clinical picture of scurvy are seldom seen these days The sporadic cases mentioned in the literature since 1945 chiefly concern elderly bachelors (10) sometimes more over, protracted strict observance of a diet prescribed for a gastro-intestinal condition leads to severe vitamin C deficiency We had occasion to study three patients with the classic clinical features of scurvy and the corresponding haemorrhagic diathesis and anaemia A detailed coagulation study was made in each case Immediately upon admission the patients were given the diet which they had followed during the year preceding hospitalization and on which they had developed scurvy This procedure made it possible to study the influence of vitamin C on haematopoiesis

Methods

Coagulation studies

The following determinations were made Platelet count platelet morphology *in smear* tourniquet test (5 min 100 *mm Hg*) *bleeding* time (12) clot retraction (21) heparin retarded clotting time (22), plasma recalcified clotting time partial thromboplastin time (18), one stage prothrombin time with human brain thromboplastin (36) whole blood clotting time (20) thrombelastography (15) prothrombin consumption index (30) thromboplastin generation test (3) glass activation test (23) factor I (fibrinogen) (6) factor II (prothrombin) factor V (proaccelerin) and factor VII complex (35) factor X (Stuart factor (2) euglobulin clot lysis time (7)

Haematological investigations

For a description of the methods we may refer to Verloop et al (42) The blood vitamin C was determined according to Roe and Kuether (38) Ascorbic acid saturation test 10 mg ascorbic acid per kg body weight is given orally in divided doses and the daily urinary excretion of ascorbic acid is determined Normally at least 50 % of the daily dose is excreted after 1—2 days

Treatment

Immediately upon admission the patients were given exactly the same diet as they had been taking during the preceding year without vitamin C supplementation Bed rest was imposed A wait and see attitude was as

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It is also known that signs of osteomalacia may appear after partial gastrectomy (2, 4, 8, 9, 12, 15), as was suggested by Ask-Upmark in 1939 (1) His description of a case of his own is instructive a pronounced osteomalacia occurred in a 38-year-old woman some years after a subtotal gastrectomy for ulcer Complete recovery followed upon administration of vitamin D (3)

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In the present study decalcification of the skeleton was demonstrable radiographically in all three patients, but there were no definite signs of osteomalacia However, the laboratory data (hypocalcemia, hypocalcuria, increase of serum alkaline-phosphatase level) and the strongly positive calcium balance after administration of vitamin D in case 2 suggested a chemical osteomalacia

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Methods

Coagula on ud e

The follow ng d erm nat ons were made Pla ele count pla elet morphology n smear ourn quet test 5 m n 100 mmHg bleed ng time (12) clot retract on (21) heparin retarded clott ng t me (22) plasma re calcified clott ng t me part al thromboplast n t me (18) one stage prothromb n t me with human bra n thromboplast n (36) whole blood clott ng t me (20) thrombelastography (15) prothromb n-consumpt on ndex (30) thromboplast n generat on test (3) glass act vat on test (23) factor I (fibrinogen) 6) fa tor II (pro hromb n) factor V (pro-acceler n) and factor VII *complex* (35) factor X (Stuart fa tor (2) euglobulin clot lys s t me (7)

Haemato og al nve t gations

For a descr pt on of the methods we may refer to Verloop et al (42) The blood v ta m n C was determ ned accord ng to Roe and Kuether 38) Ascorb c ac d saturat on test 10 mg ascorb c ac d per kg body we ght is g en orally n d vided doses and the da ly ur nary excret on of ascorb a d is deter m ned Normally at least 50 % of the da ly dose is excreted af er 1—2 da s

T ea ment

Immed a ely upon admiss on the pat ents were g ven exactly the same d et as they had been tak ng during the preced ng year w th out tam n C supplementat on Bed rest was mposed A wa t and see att tude was as

Subm ed f pub ca on February 26 1964

It is also known that signs of osteomalacia may appear after partial gastrectomy (2, 4, 8, 9, 12, 15), as was suggested by Ask-Upmark in 1939 (1) His description of a case of his own is instructive a pronounced osteomalacia occurred in a 38 year-old woman some years after a subtotal gastrectomy for ulcer Complete recovery followed upon administration of vitamin D (3)

The presence of osteomalacia is of interest since this condition can be associated with a weakness in proximal muscles, which can regress, sometimes completely, after treatment with vitamin D (7, 13, 16) Sometimes the muscular weakness can appear before any other manifestation of osteomalacia (6)

In the present study decalcification of the skeleton was demonstrable radiographically in all three patients, but there were no definite signs of osteomalacia However, the laboratory data (hypocalcemia, hypocalcuria, increase of serum alkaline-phosphatase level) and the strongly positive calcium balance after administration of vitamin D in case 2 suggested a chemical osteomalacia

A more comprehensive study on the occurrence of muscular weakness and malabsorption after partial gastrectomy has now been undertaken by the present authors

Summary

A progressive weakness in girdle and proximal limb muscles occurred in three patients, 2—8 years after partial gastrectomy for ulcer Muscle biopsies were almost normal, but the clinical picture and the electromyographical examinations suggested myopathy All patients had also signs of a malabsorption syndrome The pareses decreased in two patients given treatment with vitamin D

The muscular weakness is considered to represent a hitherto disregarded sequel of partial gastrectomy

Acknowledgement

This investigation was supported by a grant from the Swedish Medical Research Council

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three daily meals of bread and cheese or sausage he had tea sometimes Coca Cola or lemonade In July 1961 he reported to the out patient clinic in view of fatigue and pain in the calf and knee of the left leg A large haematoma had formed on the left calf There was slight anaemia B P 150/80 mm Hg The skin showed unmistakable follicular hyperkeratosis with peculiar coiling of hairs Numerous petechiae and extensive sub cutaneous ecchymoses in the left popliteal fossa and both calves The teeth were carious No gingival bleeding

In this patient the least severely affected the Hb concentration was 8 6 g/100 ml at admission the condition showed spontaneous improvement during the period of observation without treatment The haematomata were absorbed and did not recur during bed rest The Hb concentration rose to 11 5 g/100 ml The plasma vitamin C concentration remained immeasurably low After the vitamin C saturation test the Hb concentration was 12 5 g/100 ml No distinct reticulocyte crisis occurred the reticulocyte count continued to fluctuate at the slightly increased level of 30—40 per thousand

Case 3 A 38-year old bachelor living alone was found in an attic room by neighbours Both the room and the patient were in a state of indescribable squalor For years this man too had subsisted almost entirely on bread cheese and sausage He was hospitalized in April 1961 The exhausted patient was in poor nutritional condition Poor cooperation and a very distrustful disposition were striking features B P 155/95 mm Hg gingiva swollen and spongy bleeding readily when touched The skin showed follicular hyperkeratosis Numerous petechiae were seen on the legs round the hair follicles Extensive ecchymoses existed on the posterior aspect of lower legs and thighs and particularly in the popliteal fossa

This patient showed the severest vitamin C depletion and most pronounced anaemia (Hb concentration 6 7 g/100 ml) The Hb concentration after 10 days observation on the deficient diet was 6 g/100 ml (fig 2)

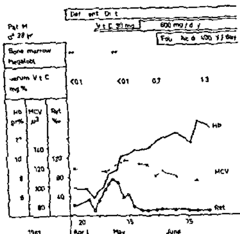


Fig 2 Case 3 Response to 30 mg ascorbic acid per day and 400 μg folic acid per day respectively in a patient with scurvy The vitamin C-deficient diet was maintained throughout the study

Treatment was then instituted with a small dose of vitamin C 3 × 10 mg orally per day (29) A reticulocyte increase to almost 80 per thousand occurred The Hb concentration rose to 10 6 g/100 ml in the course of three weeks A repeated examination of the bone marrow showed that megaloblastic changes still existed The serum folic acid concentration was unchanged 4 0 mμg/ml (at admission 4 6 mμg/ml) The FIGLU test however had become negative The vitamin C saturation test was then carried out by daily oral administration of 3 × 200 mg vitamin C The Hb concentration rose to 11 9 g/100 ml Subsequently 400 μg folic acid was intramuscularly given every day After a week the bone marrow was normoblastic and the Hb concentration had further risen No second reticulocyte crisis occurred The Schilling test was then carried out which revealed normal vitamin B_{12} absorption

Results

1 *Diagnostic features of scurvy*

The most important data on which the diagnosis of scurvy was based are presented in table 1 Each of these patients

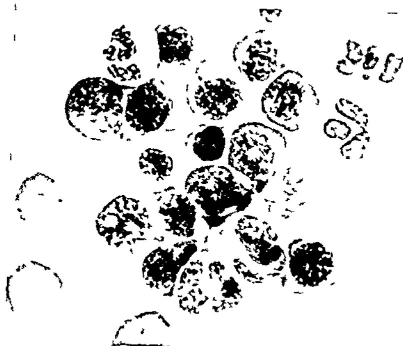


Fig 1 Case 3 Bone marrow on admission in a patient with scurvy showing overt megaloblastic erythropoiesis and giant stabs

sumed for the first 10—20 days, during which no therapy was instituted This period of observation is necessary because it has been found that bed rest alone can produce improvement of the clinical and haematological features (8, 43)

Case reports

Case 1 A 71-year old widower was admitted in June 1958 with progressive weakness and syncope, poor appetite, extensive haematomata of the legs and a painfully swollen right knee

During a brief transient period of diarrhoea three years previously, the patient stated, the family doctor had forbidden him to eat potatoes or vegetables The patient had strictly observed this dietary restriction and for three years his daily diet had been breakfast two rusks with butter and sugar and a glass of boiled milk, lunch two slices of bread with cheese or sausage and a cup of tea dinner porridge with butter and sugar

The patient was an ill, anaemic man in moderate nutritional condition, who showed little cooperation B P 135/65 mm/Hg Skin and sclerae seemed sub-icteric No gingival bleeding at the carious dental remnants The skin showed follicular hyperkeratosis Both legs, and particularly the calves and popliteal fossa showed large subcutaneous ecchymoses in various degrees of severity and absorption and petechiae The right knee-joint was swollen, probably as a result of haemarthrosis

At admission the Hb concentration was 8 3 g/100 ml, after 18 days observation on the deficient diet it was 7 8 g/100 ml The vitamin C saturation test was then carried out by daily oral administration of 550 mg vitamin C In 10 days, the Hb concentration rose to 11 6 g/100 ml while the erythrocyte diameter diminished from 8 5 μ to 7 8 μ The patient showed so rapid and spectacular mental and physical improvement that we could not dissuade him from leaving the hospital At an out patient follow up two months later (during which period he had been on a normal diet), the Hb concentration was 14 4 g 100 ml

Case 2 A bachelor aged 55 who lived alone had for a number of years eaten no complete hot meal potatoes vegetables or fruit because of poverty and indolence With his

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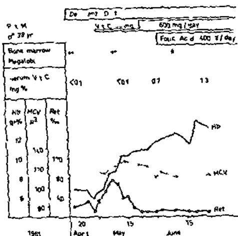


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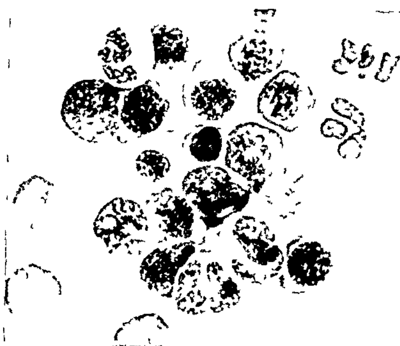


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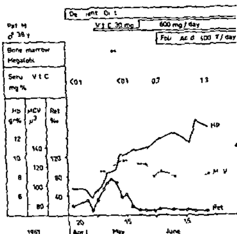


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TABLE I. Diagnostic features in 3 patients with scurvy

	Case 1 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
Bleeding gingiva	–	–	±	
Petechiae	++	+	++	
Ecchymoses	++	++	++	
Follicular hyperkeratosis	+	–	+	
Arthralgia	+	+	–	
Anaemia	+	+	++	
Vitamin C: diet (mg/day)	< 5	< 5	< 5	> 30 mg
Vitamin C: plasma (mg%)	0.1	< 0.1	< 0.1	0.4–1.2
Vitamin C saturation test (10 mg/kg body weight) (in days)	*8*	*6*	*12*	*At least 50% of daily dose excreted after 1–2 days*

TABLE II. Haematological data for 3 patients with scurvy

	Case 1 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
Blood count				
Haemoglobin (g%)	8.3	8.6	6.7	14.0–17.2
Erythrocytes (10^6/mm^3)	2.47	3.22	1.88	4.5–5.5
Haematocrit (%)	–	27.2	21.3	40–50
Mean diameter ery. (µ)	8.5	7.5	8.4	6.5–7.5
M.C.V. (c µ)	–	85	117	76–96
M.C.H.C. (%)	–	31.6	30.7	32–36
Reticulocytes (‰)	40	40	20	2–20
Leucocytes	7 600	4 100	5 200	–
Neutrophils (%)	55	75	62	–
Lymphocytes (%)	37	24	35	–
Platelets (10^3/mm^3)	476	380	152	*150–400*
Bone marrow				
Erythr. myeloc. ratio	2 : 1	1 : 1.5	1 : 1	1 : 2.5–5
Megaloblastic	±		++	–
Giant stab	–	±	++	–
Iron R.E.S.	++		++	± – +
Sideroblasts	±		+	±
Siderocytes	±		±	–

Table III Haematological data and diet of 3 patients with scurvy

	Case I 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
Serum iron (µg%)	61	72	194	133 ± 28
Unsat iron bind cap (µg%)	265	238	114	215 ± 42
Iron saturation (%)	18	26	62	38 5 ± 8 6
Serum vit B_{12} (µµg/ml) (L. Leichmannii)	–	300	200	160–1 000
Schilling test ($Co^{60}B_{12}$ %/48 hrs)	–	–	9 5	>9
Serum folic acid (mµg/ml (L. Casei)[1]	–	–	4 6	6–23
Figlu excretion[1]		–	+	–
Diet[2]				
Fe content (mg/day)	6	18	10	10–15
Folic acid content (µg/day)	55 65	99 231	21–88	~100
Vit B_{12} content (µg/day)	2	11	2	>1
Vit C content (mg/day)	< 5	< 5	5	>30

[1] Dr Mollin was kind enough to make these determinations for us (17)

[2] According to McCance (27)

Table IV Haematological data concerning haemolysis for 3 patients with scurvy

	Case 1 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
Coombs test	Neg	Neg	Neg	–
Bilirubin (mg%	*1 55*	*0 45*	1 95	<0 8
1 min %	*11*		19	<20
Haptoglob *serum* mg 100 ml serum		240	*20–30*	*30* 240
Median corpuscul fragility (% NaCl)				
Before incub	0 375	0 42	0 355	0 39 0 445
After incub		0 54	0 46	0 505–0 575
G-6 PD screening (min		*17*	*21*	22 ± 6
G.S H stability test (mg 100 ml)				
Before incub		69	60	40 110
After incub		59	50	~40
Faecal stercobilinogen (mg 24 hrs	Normal	Normal	143	<183

Nyman (34)

Motulsky et al (32

* Stevenson et al (41)

Haemolytic index increased (Miller et al 31

TABLE I Diagnostic features in 3 patients with scurvy

	Case 1 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
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Petechiae	++	+	++	
Ecchymoses	++	++	++	
Follicular hyperkeratosis	+	+	+	
Arthralgia	+	+	+	
Anaemia	+	+	++	
Vitamin C diet (mg/day)	<5	<5	<5	>30 mg
Vitamin C plasma (mg%)	0 1	<0 1	<0 1	0 4–1 2
Vitamin C saturation test (10 mg/kg body weight) (in days)	8	6	12	At least 50% of daily dose excreted after 1—2 days

TABLE II Haematological data for 3 patients with scurvy

	Case I 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
Bloodcount				
Haemoglobin (g%)	8 3	8 6	6 7	14 0–17 2
Erythrocytes (10^6/mm^3)	2 47	3 22	1 88	4 5–5 5
Haematocrit (%)	–	27 2	21 3	40–50
Mean diameter ery (μ)	8 5	7 5	8 4	6 5–7 5
M C V (c μ)	–	85	117	76–96
M C H C (%)	–	31 6	30 7	32–36
Reticulocytes (‰)	40	40	20	2–20
Leucocytes	7 600	4 100	5 200	–
Neutrophils (%)	55	75	62	–
Lymphocytes (%)	37	24	3[illegible]	–
Platelets (10^3/mm^3)	476	380	152	150–400
Bone marrow				
Erythr myeloc ratio	2 1	1 1 5	1 1	1 2 5–5
Megaloblastic	±		++	–
Giant stab	+	±	++	
Iron R E S	++		++	±–+
Sideroblasts	±		+	±
Siderocytes	±		±	–

TABLE VI Laboratory data for 3 patients with scurvy

	Case 1 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
Urine				
Urobilin	+	++	++	–
Sediment	Few erythr	Few erythr	Few erythr	–
Faeces				
Occult blood	–	–	–	–
Blood				
ESR (mm/hr)	72	60	4	<10
Total protein (g%)	7 0	6 1	5 05	7 5 ± 0 6
Albumin (relat %)	38	45	58	66 ± 7
α-glob (relat %)	20	22	16	11 ± 1 6
β-glob (relat %)	17	14	11	8 ± 2 4
γ-glob (relat %)	25	19	15	15 ± 3
PSP retention (% after 30 min)	–	4	4 5	<6
Urea (mg %)	33	30	53	20–40
Stomach				
Free acid	+	+	–	–
Histology	–	Atrophy Chronic inflammation	Atrophy Chronic inflammation	–

patient 3 it was markedly megaloblastic (fig 1) Leucocytes with giant stab nuclei were found in the bone marrow specimens from all patients (table II)

Patient 3 showed an increased serum iron concentration and increased serum iron saturation percentage Patients 1 and 2 showed a somewhat low serum iron concentration but a *normal* latent iron binding capacity of the serum (table III) not commensurate with iron deficiency There might be a disturbed utilisation of iron for haemsynthesis (iron accumulation in the reticulo-endothelial system of the bone marrow demonstrated in patients 1 and 3 table II) The serum vitamin B_{12} concentration was *normal* in patients 2 and 3 The positive FIGLU test and decreased serum folic acid concentration in patient 3 indicated a folic acid deficiency In patient 3 — with the severest degree of scurvy — increased haemolysis *would* seem to have contributed to the anaemia The serum free haptoglobin concentration was decreased *while the urobilinogen* excretion was increased (table IV)

3 *Coagulation studies*

The *tourniquet* test was negative in all cases The bleeding time was slightly pro-

TABLE V Coagulation studies on 3 patients with scurvy

	Case 1 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
Bleeding time	1 50″–2	1 15″–2	2 30″–5	1 –4
Platelet count	467,000	303 000	152 000	150 000–450 000
Platelet morph in smear	Normal	Normal	Normal	Normal
Platelet adhesiv in smear	Normal	Normal	Normal	Normal
Tourniquet test	Negative	Negative	Negative	Negative
Clot retraction after 2 hrs	58%	65%	79%	38–64%
Capillary microscopy	–	Tortuous capillaries in nailwalls	Cap dilated and tortuous Perifollicular bunches of dilated cap with faded contours	–
Heparin retarded clotting time	–	170	270	210 ± 25
Recalcif plasma clotting time	120	160	180″	140 ± 16
Whole-blood clotting time	8 30	6 35″	6 30	7 30 ± 42
Thrombelastogram r	11 45	11 20″	9 30″	12–17
k	3 50″	4 30	5 10	4–7
m e	212%	120%	85%	80–150%
Partial thromboplastin time	–	68	63″	70 ± 5 5
Prothrombin consumption index	<10%	10%	12%	<20%
Thromboplastin generation test	–	10 6″	11 0	8–11
Glass activation test	–	Normal	Normal	Normal
Prothrombin time/control	14 2 /14 2	15 3″/15 3″	17 2 /14 4″	Control ± 0 6
Factor I (fibrinogen) (mg%)	580	540	210	250–500
Factor II (prothrombin) (%)	100	100	64	88 ± 14
Factor V (proaccelerin) (%)	100	100	66	100 ± 16
Factor VII (complex) (%)	100	100	60	110 ± 20
Factor X (Stuart factor) (%)	110	100	60	104 ± 12
Euglob clot lysis time	–	360	C0	60–180

had for years subsisted on a diet practically devoid of vitamin C, which was completely or *almost completely* absent from the plasma The vitamin C saturation test carried out in a later phase of the investigation revealed pronounced vitamin C depletion of the tissues Arthralgia and general weakness were the presenting symptoms in each of these three patients

2 *Haematological data*

Pronounced anaemia existed in each case, it was hyperchromic and macrocytic in patients 1 and 3 In patient 3, moreover the mean cellular volume was unmistakably too large There was slight reticulocytosis The highly cellular bone marrow showed a hyperplastic red system in each patient In patient 1 the bone marrow showed slight megaloblastic changes, in

TABLE VI Laboratory data for 3 patients with scurvy

	Case 1 71 yrs	Case 2 55 yrs	Case 3 38 yrs	Normal
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Urobilin	+	+ +	+ +	–
Sediment	Few erythr	Few erythr	Few erythr	–
Faeces				
Occult blood	–	–	–	–
Blood				
ESR (mm/hr)	72	60	4	<10
Total protein (g%)	7 0	6 1	5 05	7 5 ± 0 6
Albumin (relat %)	38	45	58	66 ± 7
α glob (relat %)	20	22	16	11 ± 1 6
β glob (relat %)	17	14	11	8 ± 2 4
γ glob (relat %)	25	19	15	15 ± 3
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3 *Coagulation studies*

The tourniquet test was negative in all cases The bleeding time was slightly pro-

longed in only one patient The overall clotting-time determinations, recalcification time, heparin-retarded clotting time, whole-blood clotting time and the R-value in the thrombelastogram were normal in patients 1 and 2 The heparin-retarded clotting time and plasma-recalcified clotting time were on the high side in patient 3, in whom the whole-blood clotting time, partial thromboplastin time and R-value in the thrombelastogram were not abnormal Thromboplastin generation had a normal course, as indicated by the undisturbed partial thromboplastin time, prothrombin consumption and thromboplastin generation test Underlying the slight prolongation of the one stage prothrombin time in patient 3 there was a slight decrease in factors II, V, VII complex and X The anomalies seemed too slight to explain the severe haemorrhagic diathesis

4 *Other laboratory data*

X-rays of the chest and gastro-intestinal tract showed no anomalies (table VI)

Discussion

A *Clinical features*

The causes leading to a deficient diet and therefore, to the clinical features of scurvy, were characterized by McMillan and Inglis (28) as dietary ignorance, apathy and poverty This characterization applies to the present cases

The characteristic signs and symptoms of scurvy — extensive ecchymoses, purpura, articular changes, follicular hyperkeratosis, corkscrew hairs and anaemia — were all seen A striking feature was the absence of gingival bleeding — often mentioned in textbooks as the most typical symptom of scurvy Cutforth (10) previously pointed this out in his material of 11 cases of scurvy The psychological disposition in two patients was remarkable mistrust of the environment and poor co-operation The haemorrhages were localized chiefly in body parts exposed to micro-traumata and mechanical stress, i e mainly the lower extremities (1)

B *Haemorrhagic diathesis*

In spite of the severe bleeding tendency, extensive clotting studies revealed mild changes in only one patient (table V) Stefanini and Dameshek (40) pointed out that, in a number of cases of scurvy, thrombocytopenia contributes to the haemorrhagic diathesis In our three patients, however, the platelet count was normal Çetingil et al (5) believed they had demonstrated a platelet defect in a scorbutic patient In view of the normal clot retraction, normal morphology and good adhesion of platelets in a blood smear, normal thrombelastographic results and undisturbed thromboplastin generation test using platelets from the patient, a thrombopathy seems improbable

Flute and Howard (13), studying scorbutic guinea-pigs, found a coagulation defect which closely resembled the inherited deficiences of plasma thromboplastin antecedent (factor IX) and Hageman factor (factor XII) in human subjects, but differed in that it was acquired In our patients, however, no disturbance in thromboplastin generation was demonstrable the partial thromboplastin time

and R value in the thrombelastogram were not prolonged, the prothrombin consumption and the thromboplastin generation test were normal In the glass activation test of Margolis (23), activated plasma from the scorbutic patient corrected the recalcification time of intact normal plasma as well as did activated control plasma

Marx et al (25) observed a prolonged prothrombin time in scorbutic guinea pigs In patient 3, too the prothrombin time was slightly prolonged — a prolongation reflecting a mild decrease in factors II V, VII complex and X We regard it as exceedingly unlikely however that the severe haemorrhagic diathesis could be explained by this slight decrease in the concentration of a few plasma clotting factors No pathologically increased fibrinolysis was demonstrable

Aschoff (1) postulated a disturbed formation of or change in, intercellular binding substance between the endothelial cells The current emphasis however, is increasingly on the pericapillary sheath of connective tissue Lee et al (19) studied the mesenteric vessels in scorbutic guinea pigs and formed the conclusion that hypo-reactivity of the contractile vessels with dilatation and weakening of perivascular collagenous supporting structures of the venules are a causative factor (1) In that case the remarkable fact remains however that in none of our patients was the capillary resistance reduced and that the bleeding time was slightly prolonged in only one patient The absence of a correlation between the vitamin C depletion and decreased capillary resistance was noted previously by McMillan (28),

C *Anaemia*

It is remarkable that, in experimental human scurvy a test subject on a diet devoid of vitamin C for 6 months showed various signs and symptoms of scurvy, but no anaemia (9) Since scorbutic patients often have a much longer history of dietary deficiency, the test period of 6 months may have been too short

Several factors probably play a role in the aetiology of the anaemia, viz

a) First, blood loss would contribute to anaemia There was no loss of blood with the faeces in our cases, and only microscopic haematuria existed But there was certainly loss of blood in the tissues Blood loss *per se*, however, cannot explain either the severity or the type of the anaemia

b) Scurvy can be associated with increased haemolysis as was the case in our patient 3 (table IV) Goldberg (14) also offered arguments in favour of an existing hyperhaemolysis

c) As to the role of vitamin C in haematopoiesis our observations in patients 1 and 3 indicate that vitamin C exerted a stimulant influence on haematopoiesis The Hb concentration did not rise in the course of an observation period of 18 and 10 days respectively during which the scurvy diet was maintained If this scurvy diet faithfully copying these patients diets of the preceding 12 months, had contained the nutrients required for haematopoiesis (vitamin C and folic acid), then a rise in Hb concentration and a reticulocyte response would have been expected during this period of observation As it was the rise in Hb concentration and subsequent reticulocyte response did not occur until the only alteration had been made in the diet viz addition of

550 mg vitamin C per day (patient 1), and 30 mg vitamin C per day (patient 3) to the diet We feel we are justified in ascribing the improvement in haematological features to this sole alteration made in the diet administration of vitamin C (fig 2) Bronte-Stuart (4) and Cox et al (8) reached a similar conclusion

d) Some authors (16, 44) attach great importance to folic-acid deficiency in addition to vitamin C deficiency in scurvy In patient 1 and particularly in patient 3, the bone marrow showed megaloblastic changes (fig 1) In patient 3 the serum folic-acid concentration was decreased, while the FIGLU excretion in the urine was increased Serum vitamin-B_{12} concentration and vitamin-B_1 absorption were normal (table III) After 3 weeks' vitamin-C supplementation, the bone marrow in this case still showed slight megaloblastic changes The serum folic-acid concentration showed no fundamental change (4 0 as against 4 6 mμg/ml at admission) Consequently the megaloblastic changes can be ascribed to folic-acid deficiency

The FIGLU excretion became negative after vitamin C therapy It seems as if this finding might be explained by an action of vitamin C in keeping tetrahydrofolic acid in its reduced state, or by a function of vitamin C in the reduction of folic acid to tetrahydrofolic acid The latter is improbable (37) The same mechanism probably also explains the decrease in bone marrow megaloblastosis following vitamin C therapy Complete disappearance of the megaloblastic changes (fig 2) was not effected until 400 μg folic acid per day was administered (24) On the basis of animal experiments, May et al (26) and Slungaard et al (39) also concluded that there is an interaction of vitamin C and folic acid in the development of megaloblastic changes in nutritional anaemias caused by vitamin C and folic-acid deficiencies A vitamin C deficiency enhances the development of megaloblastosis in the presence of a folic acid deficiency

Nichol and Welch (33) determined the synthesis of citrovorum factor from folic acid in rat-liver sections They concluded that vitamin C facilitated the conversion of folic acid into folinic acid, and considered it reasonable to postulate that the conversion of folic acid into citrovorum factor is limited by severe vitamin C deficiency This postulate, however, has been questioned by others Doctor (11) demonstrated that the increase in urinary citrovorum factor in rats following an oral dose of folic acid is only seemingly enhanced by simultaneous administration of vitamin C The controversial findings of the above mentioned authors are possibly explained by the fact that the test animals were not deficient in vitamin-C

In a patient with scurvy, folic acid deficiency and anaemia, Zalusky and Herbert (44) observed rapid development of bone marrow megaloblastosis while the patient was on a synthetic diet without folic acid Administration of vitamin C produced no haematological improvement in blood and bone marrow A rise in Hb concentration and disappearance of the megaloblastosis occurred only after folic acid administration The discrepancy between our observations and those of Zalusky and Herbert might well be due to the severe degree of folic acid deficiency in their patient and the slight degree in ours

Summary

We have described three pat ents w th the class cal features of scurvy An extens ve rlo t ng study revealed no marked anomal es In one pat ent the bor e marrow showed pronounced megaloblastos s tl s pat ent was def c ent i fol c acid and showed s gns ind cative of hyperhaemol sis

Several factor play a role in the aetiol ogy of anaem a in scurvy The three pa t ents upon admiss on all rema ned on the same def cient d et as dur ng the pre ced ng year After vitamin C admin s tration two patients showed an un mistakable ri e in Hb concentrat on and a ret culocyte response This demonstrated a st mulat ng effect of vitamin C on eryth ropo esis In the pat ent with megaloblastos s of the bone marrow the megaloblast c changes did not completely dis appear after vitamin C treatment b t d d when fol c acid was administered

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Myelomatosis

A Clinical and Biochemical Study of 105 Cases

By

AAGE DRIVSHOLM

The first clinical account of myelomatosis (multiple myeloma) was published in 1850 by MacIntyre (42) who described mollities and fragilitas ossium. This was a classical case of the disease followed over a period of 14 months. Previously the microscopic appearance of *mollities ossium* in this patient had been described by Dalrymple in 1846 (12). The finding of a urinary protein in MacIntyre's case was reported by Bence Jones in 1848 (33). These three papers on the same case gave a very comprehensive description of myelomatosis, to which little was added until the past few decades.

The term "multiple myeloma" was introduced in 1873 by Rustizky (56) who described the pathological findings in one case of the disease. It was not however until Kahler's classical description appeared in 1889 (34) that myelomatosis was accepted as a disease *sui generis*.

After the introduction of X-rays for clinical use the disease could be diagnosed *in vivo* as reported in 1900 by Wright (68). Wright also pointed out that the cells making up the bulk of the tumour looked like the plasma cells of the bone marrow. Furthermore he suggested that the cells might originate from an abnormal proliferation of plasma cells in the marrow. After Wallgren's comprehensive study in 1920 (66) it was gradually accepted that the myeloma cells constituted a morphological entity having the characteristics of plasma cells.

Demonstration of myeloma cells in the bone marrow obtained by sternal puncture marked a new and important advance in the diagnosis of myelomatosis. The value of this diagnostic procedure was emphasized in 1931 by Zadek and Lichtenstein (69).

The behaviour of the serum proteins in myelomatosis has been the subject of

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Electrophoresis of the urine was done when proteinuria was present at the time of the diagnostic sternal puncture and in a few other cases. Concentrated urine was used either with the Tiselius technique or with paper electrophoresis by the method of Tidstrom (60).

Viscosimetry on the serum (2) at different temperatures (39—13° C) was performed in 7 cases in which cryoglobulinaemia was suspected.

Other laboratory findings are the results of routine analyses. For analyses *not* covering all 105 patients the exact number will be listed in square brackets after the analytical result.

Results and discussion

Sex ratio and age distribution

Fifty of the patients were females (48 %) and 55 males (52 %). This accords with the findings of Waldenström (65) and of Lichtenstein and Jaffe (38). In most series there has been a greater male preponderance. For instance Bayrd and Heck (6) found 64 % males (469 cases) and Breitenbucher and Hertzog (8) 75 % males (95 cases). The lower male preponderance in the present series might be due to the fact that the material is selected. In order to elucidate this aspect the author investigated the sex ratio in all deaths from myelomatosis in Denmark during the decade 1951—61 (11). In this material of 1 028 patients 53 % were males which corresponds approximately to the 52 % in the present series.

The *age distribution* is recorded in fig. 1. The youngest patient was 38 when the disease was diagnosed, the oldest 81. The largest age group was 60—69 years even when corrected for the overall age distribution of the Danish population (58). This may be compared with 70—80 years in Waldenström's series (65) and 50—60 in most others (cf. Martin 1961 (46)). The mean age at the time of diagnosis was 60.8 ± 3.1 years, not significantly lower in the γ_{1-A} group than in the group with γ_{SS} and γ_{μ} paraproteinaemia.

TABLE I. Subjective complaints in 105 cases of myelomatosis prior to confirmation of the diagnosis

Complaints	No. of cases	% of cases
Pain	76	72
Weakness	75	71
Fever	55	52
Loss of weight	47	45
Haemorrhagic diathesis	14	13
Tumour formation	4	4

Symptoms and signs

Of the 105 patients 87 (85 %) were admitted because of subjective complaints due to the myelomatosis while the remaining 15 % were admitted because of other diseases, apparently unrelated to myelomatosis. The subjective complaints *prior to admission* are listed in table I.

Pain was present in 76 cases. Fifty patients reported backache, usually in the lumbar region. Twelve had lumbago, 10 chest pain, 7 pain in the shoulders and arms, and only 2 in the lower limbs and pelvis. The sites of the pain correspond well to Innes and Newall's findings (32). Diffuse bone pain was present in 4 cases. Six patients had articular complaints including 2 with typical rheumatoid arthritis.

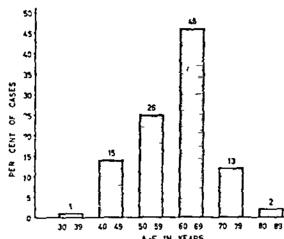


Fig 1 Distribution of 105 cases of myelomatosis by age at the time of diagnosis The figures above the columns indicate the number of patients in the group concerned

numerous publications In 1928 Perlzweig et al (54) reported hyperproteinaemia in a patient with myelomatosis However, credit is due to Freund and Magnus-Levy (18) for demonstrating that hyperproteinaemia is a common finding in this disease and is associated with an elevated ESR The occurrence of an abnormal, tall and narrow peak in the Tiselius electrophoresis pattern (M component) was first reported by Longsworth et al in 1939 (41) in 2 out of 3 patients with myelomatosis This finding has later acquired great diagnostic importance The presence of paraproteinaemia (definition, see (14)) in myelomatosis was pointed out by Grabar et al in 1956 (24) The diagnostic importance of paraproteinaemia has been emphasized by Heremans et al (30, 31) and others

Clinical studies of large materials have been reported from a number of different countries (1, 3, 4, 6, 8, 9, 10, 13, 17, 20, 21, 23, 28, 29, 32, 35, 38, 39, 43 44, 45, 46, 48, 52, 57, 65, 66, 67)

The object of the present paper is to report the results of clinical and biochemical studies on myelomatosis in a large Danish series Furthermore, results with special diagnostic methods, such as Tiselius electrophoresis and immuno-electrophoresis, will be compared with other laboratory and clinical findings

Material

The study comprises 105 cases of myelomatosis The diagnosis was based on the demonstration of myeloma cells in the marrow smears In cases of doubt, the diagnosis was secured by biopsy from a radiologically demonstrated skeletal focus or eventually confirmed by autopsy Two-thirds of the patients were admitted to Medical Department A, Rigshospitalet, Copenhagen during the period 1949—1963, while the remainder were from a number of other Danish hospitals

Methods

The results are from the time of the first sternal puncture, except for a few Tiselius and immuno-electrophoretic studies which were performed at later stages of the disease

Bone marrow studies A detailed account of the cytological studies on bone marrow specimens has been published previously (14) The term myeloma cells' as used in the present paper includes plasma cells and plasmocytic reticulum cells (14)

Tiselius electrophoresis (62) was performed on serum from all 105 patients The concentrations (in g/100 ml) of the individual protein fractions were calculated from the data (25) After electrophoresis the diffusion constant of the abnormal fraction was determined if possible (26) and the approximate molecular weight of the myeloma protein calculated

Serum immuno-electrophoresis was carried out in all cases by a method described in a previous paper (14)

months (94 patients) This corresponds to the findings of Obrecht et al (51)

Thus according to the anamnestic data, the duration of the disease prior to diagnosis varies widely This also applies to the survival time after the diagnosis has been made (*vide infra*) These findings indicate that in some cases myelomatosis may run an even, very protracted, course One of our patients who is still alive, had myelomatosis diagnosed by sternal puncture 11 1/2 years ago after having had symptoms of the disease for about 3 1/2 years

Seven of our patients had an anticomplementary Wassermann reaction (W R) for several years (maximum 8 years) before myelomatosis was diagnosed (*vide infra*) This has been reported also by Norgård (50) Other patients had a marked elevation of the E SR for years one even for 21 years (constantly > 60 mm/hour) before the diagnostic sternal puncture and for 17 years before the first symptom of myelomatosis appeared This seems to indicate that in certain cases the preclinical course may be very long

Bone marrow studies

The detailed results have been published previously (14) One patient whose myelomatosis manifested itself radiologically as so-called solitary plasmocytoma at the time of the first sternal puncture had only 3 8 % myeloma cells in the bone marrow Twenty seven months later autopsy showed small myelomatous foci in several other bones Table III gives the distribution of patients according to the percentage of myeloma cells in the bone marrow

TABLE III Distribution of 105 cases of myelomatosis according to the percentage of myeloma cells in the bone marrow smears Myeloma cells comprise plasma cells and plasmocytic reticulum cells

Myeloma cells (%)	No of cases
< 4 9	1
5 – 9 9	13
10 – 19 9	19
20 – 29 9	24
30 – 39 9	23
40 – 49 9	10
50 – 59 9	6
60 – 69 9	5
70 – 79 9	2
80 – 89 9	0
90 – 99 9	2
Total	105

smears As reported by Gormsen (22), the number of plasma cells in the normal marrow smear does not exceed 3 %

Urinary findings

Proteinuria was demonstrated (by the Heller method) in 61 of the patients at the time of the diagnostic sternal puncture (58 %) and 24 are known to have developed proteinuria at a later stage Of the patients with proteinuria 31 excreted > 1 g protein/24 hours (51 %), including 3 who excreted more than 10 g 24 hours

These results cannot be compared with those of others (7 9), as they were collected unlike those reported previously at the time of diagnosis

Electrophoresis of the urine was performed in 55 of the 61 patients *with proteinuria* Forty nine (89 %) had an abnormal fraction (M component) The 6 pa-

TABLE II Estimated duration of disease before diagnostic sternal puncture in 94 patients with myelomatosis The 3 patients in whom the duration is stated as >5 years had had their symptoms for 6, 7 and 11¾ years

Duration of symptoms (months)	No of cases	% of cases
<3	30	32
3–5	19	20
6–11	18	19
12–17	8	9
18–23	3	3
24–35	7	8
36–47	4	4
48–59	2	2
>60	3	3

Abnormal weakness was recorded in three-quarters of the cases

Febrile episodes ('*fever*') occurred in 55 cases (52 %), generally in connection with pneumonia or other infections Fifteen patients had a history of 2 or more febrile episodes

Unintended loss of weight was observed by 47 (45 %) The extent of this weight loss had seldom been recorded

Recurrent cutaneous or mucous bleeding ('*haemorrhagic diathesis*') usually in the form of violent epistaxis, had been recorded in 14 cases (13 %)

Tumour formation was observed by 4 patients Three had tumours in the sternum and the fourth one in a rib

The incidence of pain weakness fever, and loss of weight corresponds exactly to previous findings (1, 5 9, 13 36) Adams et al (1) found the incidence of the first three of these symptoms to be 68, 68, and 52 % respectively as compared with the present 72, 71, and 52 % On the other hand, these authors as well as others (17, 57) have found a higher incidence of haemorrhagic diathesis (max 39 %) than the present 13 % This difference is perhaps due to the occurrence of paramyloidosis which has been observed in 6—12 % of other series (3, 9, 38, 43, 57), but never in our autopsies

Duration of disease before diagnostic sternal puncture

An attempt was made to assess the duration on the basis of that of one or more of the above-mentioned symptoms A *reliable* assessment of the duration is impossible All the named symptoms may be due to diseases other than myelomatosis, and the onset can seldom be stated accurately by the patient Accordingly, the values merely represent an *estimate* of the duration of the disease

In 11 cases the duration is unknown (10 %) In 8 of these cases the myelomatosis was diagnosed when the patients were admitted because of other diseases

Table II lists the estimated duration of the disease prior to the diagnostic sternal puncture In 16 cases the symptoms had been present for more than 2 years (17 %), in 27 for more than one year (29 %) The longest reported duration was 11 3/4 years (pain at the site of a pathological fracture of the spine and intermittent episodes of fever), the next longest 7 years (elevation of temperature up to 40° C four times a year) Thirty patients had a duration of symptoms of less than 3 months (32 %) The arithmetic mean duration of the disease before diagnosis was found to be 12 4

months (94 patients) This corresponds to the findings of Obrecht et al (51)

Thus according to the anamnestic data the duration of the disease prior to diagnosis varies widely This also applies to the survival time after the diagnosis has been made (*vide infra*) These findings indicate that in some cases myelomatosis may run an even very protracted course One of our patients who is still alive had myelomatosis diagnosed by sternal puncture 11 1/2 years ago after having had symptoms of the disease for about 3 1/2 years

Seven of our patients had an anticomplementary Wassermann reaction (W R) for several years (maximum 8 years) before myelomatosis was diagnosed (*vide infra*) This has been reported also by Norgard (50) Other patients had a marked elevation of the ESR for years one even for 21 years (constantly > 60 mm hour) before the diagnostic sternal puncture and for 17 years before the first symptom of myelomatosis appeared This seems to indicate that in certain cases the preclinical course may be very long

Bone marrow studies

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80 89 9	0
90 99 9	2
Total	105

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These results cannot be compared with those of others (7 9) as they were collected unlike those reported previously at the time of diagnosis

Electrophoresis of the urine was performed in 55 of the 61 patients *with proteinuria* Forty nine (89 %) had an abnormal fraction (M component) The 6 pa

tients who did not have the M component excreted less than 0.5 g protein/24 hours. Only 31 of the 49 patients with an abnormal M component in the urine gave a positive Bence-Jones reaction (63 %).

Out of the patients with an abnormal M component 17 had a γ peak, 24 a β peak, and 6 an M peak of an intermediate mobility. Two patients had 2 M components (γ and β).

Electrophoresis on concentrated urine was carried out in 17 cases who showed *no proteinuria* by the Heller method. Five of these patients had an abnormal M component (29 %). During the stay in hospital 3 of the latter developed proteinuria which ceased in one case after Melphalan (N-phenylalanine mustard) therapy. The remaining 2, also treated with Melphalan, had not developed proteinuria by 1.7.1963. In no case without proteinuria by the Heller method was a positive Bence Jones reaction found.

Summing up, at the time of diagnosis an abnormal M component was found in the urine in 89 % of those with proteinuria by the Heller method and in 29 % of those without proteinuria. The Bence Jones test gave a positive result in 30 % (31 out of 105 patients). The reason why Snapper et al. (57) found Bence Jones protein in 50 % and Geschickter and Copeland (20) in 65 % as compared with our 30 % is undoubtedly that some patients develop Bence Jones proteinuria at a later stage of the disease.

Haematological findings

An *ESR* of more than 20 mm/hour was found in 101 patients. Forty seven had an ESR between 20 and 100 mm, 40 between 100 and 150 mm and 14 above 150 mm. Of the 4 patients whose ESR was below 20 mm two had reduced total protein, while the other two had normal total protein.

A reduced haemoglobin concentration (♀ < 11.7 g/100 ml, ♂ < 13.2 g/100 ml) was demonstrated in 82 patients (78 %) (no sex difference). Only 5 of these patients showed intestinal bleeding [38]. Of the 23 patients with a normal haemoglobin level 17 had been suffering from the disease for less than 3 months. However, there was no correlation between the haemoglobin level and the duration of symptoms in the patients who had had the disease for more than 3 months.

A reduced red blood-cell count (< 3.7 mill/µl in ♀ and < 4.8 mill/µl in ♂) was found in 78 [92] cases (85 %).

Leukopenia (< 3 000/µl) was found in 3, *leukocytosis* (> 10 000) in 4 patients [103].

Differential counts of leukocytes in the peripheral blood disclosed a small number of plasma cells in only 6 patients. Sixteen had an increased number of band neutrophils (> 5 %), 7 an increased number of lymphocytes (> 56 %), 5 an increased monocyte count (> 10 %) and one an increased eosinophil count (> 6 %).

Rouleau formation of the red cells was recorded in only 11 cases.

Thrombocytopenia (< 100 000/µl) was found in 20 [77] patients (26 %). Only 6 of these 20 had noticed a haemorrhagic diathesis. No patient with thrombocytopenia had leukopenia.

As already mentioned 78 % of the patients had a sub normal haemoglobin

level This is in keeping with the findings in Bayrd and Heck s (6) series These authors found leukocytosis in 5 % and leukopenia in about 35 % The explana tion of the fewness of leukopenic cases in the present series may be due to the definition of leukopenia (< 3,000/μl) Furthermore none of our patients had received any treatment when these counts were done As pointed out by Gormsen (22) the leukocyte count often decreases in the course of the disease, as a result of treatment

The number of patients having throm bocytopenia (26 %) is identical with that reported in other series (13)

Serum protein studies

Tiselius electrophoresis was carried out in all cases The stated concentrations of total protein albumin and M protein are derived from this study The lower limits for normal albumin and γ globulin were taken to be 3 5 g/100 ml and 0 94 g 100 ml respectively (27)

A *total protein* exceeding 8 g/100 ml was found in 78 patients (74 %) Of these 78 patients 67 had a reduced *albu min* concentration (89 %)

An *M component* was demonstrated in 95 patients (90 %) by Tiselius electro phoresis

Electrophoretic mobility of M components In 58 cases (61 %) the M component had a γ mobility in 30 cases (32 %), a β in 6 cases an intermediate (β – γ) and in one case an α mobility (published previously (61))

No correlation was found between the concentration of M protein and the percentage of myeloma cells in the bone marrow specimens This accords with the findings of Mandema (44)

Patients without an M component in the serum Ten patients without an M component in the serum had a total protein of less than 8 g/100 ml Out of this group 9 had a γ globulin concentration of less than 0 94 g/100 ml Urinary electrophoresis was carried out in 7 of the 10 cases, and M protein was found in the urine of 4 Thus, 3 patients did not have M protein, either *in the serum or in* the urine This is in accordance with the findings of Ossermann (52) and Harboe (26)

Paper electrophoresis (veronal buffer, pH 8 6 ionic concentration 0 125) was carried out in 54 cases An abnormal fraction was found in 48, but in several of these cases a very careful examination was needed to disclose the M component The 6 patients without an abnormal fraction did not show any M fraction on Tiselius electrophoresis Thus paper electrophoresis is as suitable as Tiselius electrophoresis in diagnosing myelomatosis but offers less scope for quantitative assessment of the abnormal fraction

Immuno-electrophoresis Paraproteinaemia was found in all 105 cases Consequently a paraprotein seems to be present in all cases of myelomatosis However the presence of paraproteinaemia is not pathognomonic (31) and the diagnosis depends on the demonstration of myeloma cells as emphasized int al by Gormsen (22)

Table IV sets out the findings for para protein A more detailed account has been published previously (14) The γ_{ss} paraprotein component moved slowly in 26, showed intermediate mobility in

tients who did not have the M component excreted less than 0 5 g protein/24 hours *Only 31 of the 49 patients with an abnormal M component in the urine gave a positive Bence-Jones reaction (63 %)*

Out of the patients with an abnormal M component 17 had a γ peak, 24 a *β peak, and 6 an M peak of an intermediate mobility* Two patients had 2 M *components (γ and β)*

Electrophoresis on concentrated urine was carried out in 17 cases who showed *no proteinuria* by the Heller method Five of these patients had an abnormal M component (29 %) During the stay in hospital 3 of the latter developed proteinuria which ceased in one case after Melphalan (N-phenylalanine mustard) therapy The remaining 2, also treated *with Melphalan, had not developed proteinuria* by 1 7 1963 In no case without proteinuria by the Heller method was a positive Bence-Jones reaction found

Summing up, at the time of diagnosis, an abnormal M component was found in the urine in 89 % of those with proteinuria *by the Heller method and in* 29 % of those without proteinuria The Bence-Jones test gave a positive result in 30 % (31 out of 105 patients) The reason why Snapper et al (57) found Bence-Jones protein in 50 % and Geschickter and Copeland (20) in 65 % as compared *with our 30 % is undoubtedly* that some patients develop Bence-Jones proteinuria at a later stage of the disease

Haematological findings

An ESR of more than 20 mm/hour was found *in 101 patients* Forty-seven had an ESR between 20 and 100 mm, 40 *between 100 and 150 mm, and 14 above* 150 mm Of the 4 patients whose ESR was below 20 mm, two had reduced total protein, while the other two had normal total protein

A reduced haemoglobin concentration (♀ < 11 7 g/100 ml, ♂ < 13 2 g/100 *ml)* was demonstrated in 82 patients (78 %) *(no sex difference) Only* 5 of these patients showed intestinal bleeding [38] Of the 23 patients with a normal haemoglobin level 17 had been suffer*ing from the disease for less than* 3 months However, there was no correlation between the haemoglobin level and the duration of symptoms in the patients who had had the disease for more than 3 months

A reduced red blood cell count (< 3 7 *mill/μl in ♀ and* < 4 8 *mill/μl in ♂*) was found in 78 [92] cases (85 %)

Leukopenia (< 3,000/μl) was found in 3, *leukocytosis* (> 10,000) in 4 patients [103]

Differential counts of leukocytes in the peripheral blood disclosed a small num*ber of plasma cells in only* 6 patients Sixteen had an increased number of band neutrophils (> 5 %), 7 an increased number of lymphocytes (> 56 %), 5 an increased monocyte count (> 10 %), and one an increased eosinophil count (> 6 %)

Rouleau formation of the red cells was recorded in only 11 cases

Thrombocytopenia (< 100,000/μl) was found in 20 [77] patients (26 %) Only 6 of these 20 had noticed a haemorrhagic diathesis No patient with thrombocytopenia had leukopenia

As already mentioned, 78 % of the patients had a sub normal haemoglobin

level This is in keeping with the findings in Bayrd and Heck's (6) series These authors found leukocytosis in 5 % and leukopenia in about 35 % The explanation of the fewness of leukopenic cases in the present series may be due to the definition of leukopenia (< 3 000/µl) Furthermore none of our patients had received any treatment when these counts were done As pointed out by Gormsen (22) the leukocyte count often decreases in the course of the disease, as a result of treatment

The number of patients having thrombocytopenia (26 %) is identical with that reported in other series (13)

Serum protein studies

Tiselius electrophoresis was carried out in all cases The stated concentrations of total protein albumin and M protein are derived from this study The lower limits for normal albumin and γ globulin were taken to be 3 5 g/100 ml and 0 94 g/100 ml respectively (27)

A total protein exceeding 8 g/100 ml was found in 78 patients (74 %) Of these 78 patients 67 had a reduced *albumin* concentration (89 %)

An M component was demonstrated in 95 patients (90 %) by Tiselius electrophoresis

Electrophoretic mobility of M components In 58 cases ([illegible] %) the M component had a γ mobility in 30 cases (32 %) a β in 6 cases an intermediate (β γ) and in one case an α mobility (published previously (6))

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Table IV sets out the findings for paraprotein A more detailed account has been *published* previously (14) The γ_{SS} paraprotein component moved slowly in 26 showed intermediate mobility in

TABLE IV Distribution of 105 cases of myelomatosis by type of paraprotein in the serum The 10 patients with γ_{SS} and γ_{μ} paraprotein (10) and the 2 patients with γ_{1A} and γ_{μ} paraprotein (2 *) appear twice

	Associated components					
Type	None	γ_{SS}	γ_{1A}	γ_{1M}	γ_{μ}	Total
γ_{SS}	57	2	0	0	10	69
γ_{1A}	24	0	0	0	2	26
γ_{1M}	1	0	0	0	0	1
γ_{μ}	*8*	*10*	*2*	*0*	*1*	21

TABLE V Distribution of 105 cases of myelomatosis according to immuno electrophoretic studies The normal immunoglobulins (I G) comprise the fractions γ_{SS} γ_{1A} and γ_{1M} The patients in groups 0—III are divided into cases with or without a history of febrile episodes

	No of decreased I G fractions			
	0	I	II	III
Fever	3	5	25	22
No fever	*2*	*4*	*19*	*25*
Total	5	9	44	47

28, rapid mobility in one, and β mobility in 16 patients

An evaluation of immunoglobulin, assessed on the basis of the immuno electrophoretic appearances, is shown in table V In 91 cases (87 %) a reduction in the quantity of 2 or 3 of the normal immunoglobulins (fractions γ_{SS}, γ_{1-A}, and γ_{1-M}) was found The same table gives the number of patients with and without a history of febrile episodes As is apparent from the table, the immuno-electrophoretic data regarding the quantity of immunoglobulins appear to be of no value in evaluating the tendency to infections

Types of paraproteinaemia and febrile episodes A history of febrile episodes was given by 8 [24] patients of the γ_{1-A} paraprotein group (33 %) and by 33 [59] of the γ_{SS} group (56 %), by 5 [9] of the γ_{μ} group (56 %), and by the one patient who had γ_{1-M} paraproteinaemia The above values include only patients with a single paraprotein in the serum [93] Thus, febrile episodes had occurred in fewer cases of the γ_{1-A} group than of groups γ_{SS} and γ_{μ} Fahey et al (15) found the same tendency to infection in all three groups Their investigations, however, comprised febrile as well as afebrile infections and therefore cannot be compared directly with the present study

γ_{μ} paraproteinaemia and M component in the urine As already mentioned 21 patients had γ_{μ} paraproteinaemia (Bence-Jones protein in the serum) Urinary electrophoresis was carried out in 16 of the 21 cases and showed an M component in 14

In anticomplementary Wassermann reaction was found in 7 [97] patients (7 %), all of whom had paraproteinaemia of the γ_{SS} type Six of these patients had a total protein > 10 g/100 ml and two > 15 g/100 ml

Cryoglobulinaemia was demonstrated in 4 of the 7 investigated cases

Calcium metabolism

Serum calcium was determined in 68 cases Eighteen showed values exceeding *11 0* mg/100 ml (26 %), including 5 cases

having more than 14 7 mg/100 ml Two of the latter five patients showed cerebral confusion at the time of the study After prednisone therapy the mental confusion subsided in parallel with the decrease in serum calcium

Seven of the patients with hypercalcaemia had γ_{1-A} paraproteinaemia The frequency of γ_{1-A} paraproteinaemia in the group studied being 24 % (corresponding to the frequency in the entire series), hypercalcaemia is about 1 1/2 times more common in the γ_{1-A} group than in the group of γ_{SS} and γ_{μ} paraproteinaemia

An impaired renal function was found in 6 of the patients with hypercalcaemia This corresponds to the frequency in the entire series

A serum calcium level < 8 3 mg/100 ml was found in 2 patients There was no correlation between the serum calcium and albumin concentration or between the calcium and total protein values

Serum phosphate was investigated in 54 patients In 11 the values were > 4 7 mg P/100 ml (20 %) and in one > 2 5 mg P/100 ml Eight of the 11 patients with hyperphosphataemia had impaired renal function

Alkaline phosphatase values of more than 11 King Armstrong units were found in 13 cases (5 with hyper- 6 with normo- and 2 with hypocalcaemia) Only one patient exhibited the triad hypercalcaemia hypophosphataemia and elevated alkaline phosphatases which is characteristic of hyperparathyroidism

The urinary excretion of calcium was determined in 12 patients An increased output (♀ > 300 mg ♂ > 250 mg 24 hours on a normal diet) was found in 6, one of whom had hypercalcaemia and 3 impaired renal function

Sulkowitch's test was carried out in several cases However, since this test does not give a quantitative measure of the urinary output of calcium (cf Ritter et al (55)), the results are not included

The number of patients with hypercalcaemia (26%) is not in exact conformity with the findings of Bayrd and Heck (5) and Ghormley and Pollock (21) who found 19 % Snapper et al (57), on the other hand, found 34 % The explanation of this difference may be that the calcium values were determined at different stages of the disease A number of our patients developed hypercalcaemia after the disease was diagnosed Owing to the pronounced decalcification of the bones in most cases of myelomatosis (*vide infra*) hypercalcaemia and hypercalcuria might be expected to be common findings However the urinary output of calcium, determined in only 10 % of our cases does not permit any conclusions

Renal function

Serum creatinine was elevated (> 1 3 mg/100 ml) in 22 of 50 cases studied (44 %) In 17 of these patients [21] electrophoresis of the urine revealed an M component (81 %) Ten of these 22 patients had γ_{1-A} paraproteinaemia (45 %)

Blood urea was used as a measure of renal function in 41 of the 55 patients in whom creatinine was not determined Values exceeding 45 mg/100 ml were found in 16 (39 %) An abnormal M component in the urine was found in 8 of 10 tested patients with elevated blood urea Four

of the patients having a blood urea exceeding 45 mg/100 ml had γ_1–κ paraproteinaemia (25 %).

Thus judging by serum creatinine or blood urea 38 [91] of the patients (12 %) had impaired renal function. At a later stage impairment of renal function was recorded in another 13. This fact perhaps explains why Adams et al (1) and Bayrd and Heck (6) found higher frequencies of renal impairment (57 % and 60 %).

In 80 % of the cases showing impairment of renal function an abnormal M component was found by electrophoresis of the urine and in 37 % paraproteinaemia of the γ_1–κ type could be demonstrated. Since the frequency of γ_1–κ paraproteinaemia in the entire series is 25 %, impairment of renal function is about 1 1/2 times more common in myelomatosis of the γ_1–κ group than in the group of γ_{ss} and μ paraproteinaemia.

Radiological findings

Radiological signs of myelomatosis in the form of fractures or moth eaten bones were demonstrated at the time of the diagnosis in 71 [103] of the patients (69 %). Out of the remaining 32 twelve had *halisteresis*. *Ten of these 32* later developed radiological signs of myelomatosis. Osteosclerosis was not observed.

Fractures were demonstrated at the time of the primary radiography in 59 patients (57 %); in 32 [95] the fractures were of the dorsal spine (34 %), in 26 [97] of the lumbar spine (27 %) and in 5 of the ribs. In a very few cases fractures were seen in the cervical vertebrae or long bones.

Myelomatous infiltrations (without fractures) were found at the time of diagnosis in 52 (50 %), involving the skull in 33 [90] or 37 %, the pelvis in 18 [68] or 26 %, and the long bones in 16 [35]. Fourteen had radiological changes of the ribs, 10 of the spine, and a very few of the mandible, scapula, clavicles or sternum.

All 13 patients with hypercalcaemia showed halisteresis. Twelve of these patients had fractures and 12 moth eaten bones.

The incidence of radiological changes in the present series matches that reported by others (1, 4, 5, 9, 36).

Other objective findings

Adenitis was demonstrated in 9 patients, *hepatomegaly* in 8, and *splenomegaly* in 3. Only 2 patients had hepato-splenomegaly and only one all three abnormalities.

The aetiology of these alterations might be infiltration of these organs with myeloma cells, as such infiltrations are very common in myelomatosis (57). Presumably these infiltrations are smaller *at the time of diagnosis* than later in the course of the disease. This assumption might explain why the frequency of adenitis, hepato- and splenomegaly is lower in the present study than in others (20, 57). For instance Snapper et al (57) found hepatomegaly in 40 % and hepato splenomegaly in 23 %.

Cutaneous and mucous bleeding was observed in 10 patients, 4 of whom had a prolonged bleeding time and one a low prothrombin proconvertin value. In the

remaining cases there was no explanation of the haemorrhagic diathesis

Neurological findings (pareses and reflex disturbances) were demonstrated at the time of admission in 8 patients In all these fractures were found in the affected regions

Treatment

Treatment (radiation, cytotoxic drugs, and corticosteroid) was given in 92 cases (88 %)

Melphalan (N phenylalanine mustard) was administered to 32 of the patients The preliminary results of this treatment which seem extremely promising have been published by Videbæk (64) The influence of the drug upon the survival time cannot yet be analysed Therefore Melphalan treated patients were not included in the prognostic study (*vide infra*)

Radiation in the form of intensive X ray treatment of local lesions was used in 61 cases in 50 of whom the radiation was combined with other forms of treatment

Urethane was administered to 35 *corticosteroid* to 34 patients A combination was used in 16 cases

Treatment with other types of cytotoxic drugs had been given in 16 cases None of these cytotoxic drugs are used any longer in this country for the treatment of myelomatosis The 16 patients are not included in the prognostic studies

Effect of treatment

In an effort to evaluate the therapeutic effect the patients were divided into groups according to the treatment received (table VI) The duration of the disease (from the time of diagnosis until death) was compared in the individual groups The duration of the disease (D D) in each individual case was calculated in months In the statistical calculations however D D is replaced by the quantity $\log_{10}$ (D D) as these values in the present material show a normal distribution in all the groups (table VI)

Group I No treatment This group comprises 11 of the 13 untreated patients Two cases including one with malignant hypertension were considered beyond hope at the time of the diagnostic sternal

TABLE VI Distribution of 48 cases of myelomatosis by treatment The duration of the disease (D D) in the individual patients is calculated from the time of diagnosis until death The mean duration of the disease in the individual groups is stated as $\log_{10}$ (D D in months) The group miscellaneous comprises partly patients treated with corticosteroid or urethane and partly patients treated with combinations of corticosteroids urethane and radiation The difference between the mean of $\log_{10}$ (D D) in the 4 groups is not significant ($P > 0.1$) Cf also text

Group	No of cases	Treatment	Mean of $\log_{10}$ (D D)
I	11	0	0 89 ± 0 39 (SD)
II	11	Radiation to myeloma foci	0 87 ± 0 64 (SD)
III	10	Radiation and urethane	1 05 ± 0 54 (SD)
IV	16	Miscellaneous	1 01 ± 0 43 (SD)

puncture and were, therefore, excluded from the group

Group II This group comprises 11 patients

Group III Radiation + urethane This group comprises 10 patients

Group IV Miscellaneous This group comprises 16 patients, treated with corticosteroid [1], urethane [3], corticosteroid + urethane [5], corticosteroid + + urethane + radiation [4], and corticosteroid + radiation [3] Three patients who were treated for less than a week before death were excluded from the group

The Melphalan group will be evaluated in a separate paper

A comparison of $\log_{10}$ (D D) in the groups II, III, and IV with group I (cf table VI) shows that the minor differences between the individual groups are insignificant ($P > 0.1$)

It must be concluded, therefore, that the mean duration of the disease in the present material was the same in untreated patients and in patients treated *with radiation urethane, and corti*costeroids This is in keeping with the findings of previous authors in larger series (5, 17, 36, 47, 49, 51 53, 57) A few authors, however have found massive urethane therapy (37, 40) and radiation (19, 35) to prolong the duration of the disease In most cases, however, the different forms of treatment *had an effect upon subjective complaints* as well as clinical findings

Prognosis

These studies included the 48 patients who make up the above 4 groups (cf table VI) The arithmetic mean duration of the disease, calculated from the time of diagnosis until death, in these 48 cases was 16 3 months (range 0 8—96 months)

By July 1, 1963, 83 of the patients (79 %) had *died* Out of the remaining 22, 18 are on Melphalan The remaining 4 patients are too few as a group to *allow any conclusions For this reason,* they are not included in the prognostic study

Type of protein and prognosis Classification of the 48 patients according to type of paraprotein gives one group of 12 having γ_{1-A} paraproteinaemia (25 %) and another of 36 having $\gamma_{SS} + \gamma_{1M}$ paraproteinaemia (75 %) This cor*responds to the distribution in the entire* series [105] The mean logarithmic duration of the disease in the γ_{1-A} group was 0 69 ± 0 35 S D as compared with 1 05 ± 0 50 in the group of $\gamma_{SS} + \gamma_{1M}$ paraproteinaemia This difference is significant ($P < 0,05$) Thus, the prognosis is poorest for patients *having* γ_{1-A} paraproteinaemia This does not *appear to have been demonstrated pre*viously

No significant differences were found in the mean logarithmic duration of the disease between

(1) *Males* [26] and *females* [22] (0 93 ± 0 54 and 0 99 ± 0 54 respectively) This corresponds to the findings of Obrecht et al (51) and of Videbæk and Johansen (63) In contrast, Feinleib and MacMahon (16) and Heinivaara and Eisalo (29) claim that women have a better prognosis than men

(2) 28 patients *with* and 20 *without proteinuria* (0 82 ± 0 49 and 1 15 ± 0 43 respectively)

(3) 20 patients *with* and 6 *without M protein in the urine* (0 82 ± 0 55 and 0 98 ± 0 46 respectively)

(4) 15 patients *with* and 23 *without impairment of renal function* (0 82 ± 0 54 and 1 01 ± 0 41 respectively)

(5) 15 patients *with a* β and 30 *with a* γ *fraction in the serum in Tiselius electrophoresis* (0 80 ± 0 40 and 1 08 ± 0 51 respectively)

(6) 5 patients *with* and 19 *without hypercalcaemia* (0 75 ± 0 35 and 0 95 ± ± 0 18 respectively)

(7) 35 patients *with* and 12 *without myelomatous infiltrations* (fractures and/or moth eaten" bones) on the X ray films (0 91 ± 0 45 and 1 09 ± 0 62 respectively)

There was *no correlation* between the *duration of the disease* and (1) the *haemoglobin level*, (2) the *percentage of myeloma cells* in the sternal punctate, and (3) the *concentration of M protein* assessed by Tiselius electrophoresis

Autopsy findings

Autopsy was carried out on 37 [83] patients (45 %)

Myeloma kidney with precipitates of hyaline looking masses in the tubules and foreign body reaction was demonstrated in 12 patients (33 %)

Infiltration with myeloma cells was found in several viscera of 6 patients One patient had a myelomatous infiltration in the skin and another one in the psoas muscle

"*Solitary plasmocytoma* was found only in one patient who was admitted for and died of malignant hypertension One patient with presumed "solitary plasmocytoma had several infiltrations in the ribs Several patients who had a solitary myelomatous infiltration at the time of the diagnosis developed further osseous infiltrations during the course of the disease As emphasized by int al van Dommelen (13) a 'solitary plasmocytoma' should probably be interpreted as an initial phase of myelomatosis

Carcinoma was found in 2 patients, a stomach cancer in one and a bronchial cancer in the other Both had, in addition myelomatous infiltrations in several bones, confirmed by microscopic examination

Paramyloidosis was not demonstrated by the use of the current special staining methods It is impossible to explain why paramyloidosis did not occur in this series, but it may be mentioned that Teilum (59) did not find any case of myelomatosis with paramyloidosis in a major Danish autopsy series

Summary and conclusion

The clinical and biochemical changes in 103 cases of myelomatosis are described The diagnosis was based in all cases on the demonstration of myeloma cells in the bone marrow All investigations are from the time of the diagnostic sternal puncture

In all 103 cases paraproteinaemia was found by immunoelectrophoresis which thus affords valuable aid in the diagnosis of myelomatosis 25 % of the patients had a γ_{1-A} (β_{2A}) paraprotein Of this group 33 % had a history of febrile episodes before admission, as compared with 56 % of the patients with paraproteinaemia of the γ_{ss} and γ_{M} types Hypercalcaemia and an impaired renal

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These studies included the 48 patients who make up the above 4 groups (cf table VI) The arithmetic mean duration of the disease, calculated from the time of diagnosis until death, in these 48 cases was 16 3 months (range 0 8–96 months)

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(2) 28 patients *with* and 20 *without proteinuria* (0 82 ± 0 49 and 1 15 ± 0 43 respectively)

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function were about 1 1/2 times as common in the γ_{1-A} type as in myelomatosis of the $\gamma_{ss} + \gamma_{\mu}$ types

Serum electrophoresis by the Tiselius technique was of diagnostic significance in 90 % of the cases Paper electrophoresis afforded the same diagnostic aid Thus, immuno electrophoresis seems to be of greater diagnostic value than paper and Tiselius electrophoresis in myelomatosis The advantage of the latter two methods over immuno-electrophoresis is that they afford quantitative data regarding the individual protein fractions

Proteinuria was present in 58 % of the cases An abnormal M component, found by paper or Tiselius electrophoresis, was demonstrated in the concentrated urine in 89 % of those who had proteinuria and in 29 % of those who did not show proteinuria by the method of Heller The Bence-Jones reaction gave a positive result in 30 % of all the patients

Radiological signs of myelomatosis were primarily present in 69 % of the patients, in 57 % in the form of fractures A so-called 'solitary plasmocytoma' was found in one patient who died of malignant hypertension shortly after the myelomatosis had been diagnosed

Paramyloidosis was not found in any of 37 autopsies

The arithmetic mean duration of symptoms before diagnostic sternal puncture was calculated to be 12 4 months (range 24 hours — 11 1/2 years)

The arithmetic mean duration of the disease, calculated from the time of diagnosis until death, was 16 3 months (range 0 8—96 months) Thus, a few cases of myelomatosis run a protracted *clinical* course The demonstration of a permanent elevation of ESR to more than 60 mm/hour in one patient 17 years before the first symptom of myelomatosis appeared and of an anticomplementary Wassermann reaction in 7 patients for up to 8 years before the diagnosis indicates that myelomatosis may also have a long *preclinical* course

Prognostic studies revealed that radiation to isolated skeletal foci and systemic treatment with urethane and/or corticosteroid had no influence upon the mean logarithmic duration of the disease, although a subjective as well as a clinical effect was repeatedly noted Moreover, it was found that patients with myelomatosis of the γ_{1-A} type have a poorer prognosis than patients having type γ_{ss} or γ_{μ} paraproteinaemia The influence of the disease cannot yet be assessed, but the preliminary results appear to be promising

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Centrilobular Hepatic Necrosis in Cardiac Failure

One Case with Severe Acute Jaundice

By

Hermod Gadeholt and Jostein Halgen

Moderate jaundice due to cardiac cirrhosis is commonly observed in patients with chronic congestive heart failure Extreme jaundice is, however, seldom reported in these patients The paper deals with acute hepatic insufficiency and very high serum bilirubin values in a patient suffering from congestive heart disease

Case report

A 37 year-old dock worker was admitted to the hospital on Sept 19 1962 He was treated for rheumatic fever at the age of 12 but had no history of jaundice The patient had enjoyed a good health until Nov 1961 when he got a cold with rust-colored sputum He was admitted to hospital Aortic stenosis and incompetence and mitral stenosis were diagnosed and verified with cardiophonography There were no signs of hepatic insufficiency He was discharged without cardiac symptoms and without need of medical treatment He continued to work hard without any complaints until one week prior to admission when he suddenly became ill with nausea vomiting and upper abdominal pain Three days later he developed jaundice and fever Tea colored urine and clay-colored stools were observed

On admission nausea jaundice and slight edema of the ankles were present Pulse 90 regular Temperature 37 2° C B P 140/60 mm Hg Considerable cardiomegaly was present as were murmurs consistent with aortic stenosis and insufficiency and mitral stenosis The liver edge was palpated 2 cm below the right costal margin The chest roentgenogram showed cardiomegaly without specific chamber enlargement and an increase in the pulmonary vascular markings The electrocardiogram showed changes compatible with left ventricular hypertrophy

Laboratory findings are given in table I Three blood cultures were negative as were serological tests of Weil s disease

The patient was treated with digitalis and trichlormethiazide However he rapidly developed marked cardiac insufficiency with severe edema A decrease in blood pressure to 110/50 was observed simultaneously with a derangement of the serum electrolytes Treatment with 150 mg cortisone daily and prophylactic penicillin and tetracycline were instituted The edema decreased the level of glutamicoxalacetic transaminase (SGOT) fell from 220 units to normal values and the

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Fig 1 Photomicrograph demonstrating centri lobular hepatic necrosis of grade C H F (× 180)



Fig 2 Reticulin stains shows some condensation at the lobular centre (× 180)

Histological examination of the lungs showed an excess of iron pigment macrophages and the lower lobe of the right lung showed thrombi and pulmonary infarction

Discussion

On admission the jaundice dominated and the cardiac insufficiency was moderate Clinical diagnosis was uncertain and difficult Nothing in the history in dicated intoxication or infectious hepa titis The laboratory findings excluded Weil s disease and septicemia as well as hemolytic jaundice The liver function tests allowed no conclusions as regards obstructive or parenchymatous jaundice The combination of severe congestive heart failure and the laboratory findings led to the diagnosis of centrilobular hepatic necrosis although peripheral shock was not observed This diagnosis was verified at post *mortem* examina tion

Previous reports (1 2) have empha sized inadequacy of oxygen supply to the liver cells in the genesis of centri lobular hepatic necrosis The liver cells at the centre of the lobule receive blood at a lower oxygen tension than those at the periphery The oxygen supply to the liver cells decreases with decreasing cardiac output, but other factors such as low oxygen saturation and anemia may be involved The development of centrilobular hepatic necrosis has also been reported in conditions with severe hypotension It is, however supposed to be an adaptation to reduced cardiac output in patients with chronic left ventricular outflow ob truction They maintain peripheral blood pressure above shock level but serious reduction of the oxygen supply to the liver occurs (2)

Increased pressure in the hepatic veins might also be conducive to the centri lobular necrosis as reported in patients with constrictive pericarditis A com mon finding in these cases is cardiac cirrhosis, and a mixed picture may be seen (3)

Sherlock (3 4) demonstrated a rela tion between the extent of hepatic necrosis and the serum bilirubin levels In eight of 50 patients with congestive heart failure she found serum bilirubin values

TABLE I Laboratory findings

	Date						
	9/19	9/26	10/2	10/9	10/16	10/23	10/26
Hematological findings							
Hemoglobin (g/100 ml)	18 4	14 4	14 4	12 1	–	10 4	–
Erythrocytes (mill /mm³)	5 63	4 62	4 37	4 0	–	3 39	–
SER (mm/h)	1	1	1	31	42	84	55
Bilirubin (mg/100 ml)							
Total	8 2	–	–	26 8	14 6	–	15 0
Direct reacting	5 5	–	–	15 6	9 1	–	9 8
Icterus index	41	–	141	115	51	–	93
Thymol turbidity (McLagan U)	2 6	2 6	1 8	3 2	2 3	–	5 1
Phosphatase alkaline (Bodansky U)	2 1	3 5	3 2	4 2	5 8	–	9 4
Prothrombin (%)	40	42	55	71	80	–	45
SGOT (units/ml)	220	–	–	74	40	–	–
Sodium (mEq/l)	113	120	122	122	122	122	–
Potassium (mEq/l)	6 0	4 0	3 4	5 0	5 1	5 1	–
Chlorides (mEq/l)	74	82	87	90	84	84	–
Albumin (g/100 ml)	3 2	–	2 8	2 3	–	–	–
Urea nitrogen (mg/100 ml)	–	284	150	210	91	94	–
Creatinine (mg/100 ml)	–	2 2	–	2 3	1 5	–	–
Urinary findings							
Urobilin (Schlesinger s test)	1/40+	1/30+	1/80+	1/100+	1/120+	–	–
Bile (Harrison s spot test)	–	+	+	+	+	–	–

prothrombin content rose The serum bilirubin increased, however and reached a maximal value of 26 8 mg/100 ml after two weeks of treatment The cortisone dose was now gradually reduced to 50 mg daily and the serum bilirubin level fell to 14 6 mg 100 ml

Five weeks after admission the condition of the patient again deteriorated with shortness of breath, tachycardia and considerable edema, and he died on Oct 26 1962

At autopsy the heart was greatly enlarged and weighed 960 g showing old rheumatic endocarditis with aortic and mitral valve involvement The pericardium was thickened and adherent Fibrous adhesions were found predominantly in the left pleural cavity where the pulmonary tissue showed superficial necroses The lungs, liver, spleen and kidneys showed passive congestion The liver weighed 1 900 g

Histological examination (Dr J Lamvik The Gade Institute Dept of Pathology) of the liver showed the lobules to be intact with a gross centrilobular necrosis of the liver cells The central veins were surrounded by reticulin condensation and increased connective tissue formation Golden green pigment was found in and around the liver cells There were signs of moderate cardiac cirrhosis but no evidence of hepatitis or other abnormalities The centrilobular necrosis and the liver damage were graded as of extent C according to the Sherlock system (3 4) A photomicrograph of a representative hepatic lobule is shown in figs 1 and 2

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From Medical Department A (Head K Brochner Mortensen M D), Rigshospitalet, University of Copenhagen, Copenhagen Denmark

On the Size of Normal Human Reticulocytes

By

Sven-Aage Killmann

Recent studies by Brecher and Stohlman have shown that reticulocytes formed in response to severe hemolysis or abrupt bleeding are much larger than normal red cells (7, 8) These data support the concept formulated by Stohlman (27) that erythropoietic stimulation involves skipped divisions in erythroid precursors Moreover these studies again focus attention on the size of reticulocytes in the normal steady state of red cell production So far, data on the size of normal reticulocytes have been limited to measurements of cell diameters in blood smears (20 21) It was the aim of the present study to re investigate the size of normal reticulocytes by a method which avoids some of the short comings of previous measurements

Method

Venous blood was drawn from seven healthy males age 20—40 years A few drops of oxalated blood were mixed with 0 15 % brilliant cresyl blue in isotonic saline One drop of the mixture was placed between a slide and a coverslip The preparations were observed under a Zeiss photomicroscope, with oil immersion and 1 000 × magnification In each blood sample 30—35 fields containing a reticulocyte were photographed The vast majority of the reticulocytes were mature i e they showed only a faint reticulum Enlargements of the photographs were made on glossy paper with a final magnification of approximately 4 000 × Prints with blurred cell outlines (resulting mainly from cell movements during exposure) were discarded In the remaining prints the area of the reticulocytes was determined planimetrically with an OTT Kompensations Polarplanimeter For each reticulocyte an adjacent non reticulated red cell was measured on the same print In each measurement the outline of a cell was traced five times and the resulting planimetric reading recorded (thus the actual area of the cells is one fifth of the values shown in table I)

To estimate reproducibility five reticulocytes were measured five times each as indicated above The coefficient of variation ranged from 0 41 to 0 98 %

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greater than 4 mg/100 ml, and the three highest values were 18 0, 21 5 and 22 0 mg/100 ml Seven of those eight patients had mitral stenosis In all grades of liver damage the serum-bilirubin level was highest in cases with pulmonary infarction The clinical laboratory and post-mortem findings in our case accorded well with these observations of Sherlock

Summary

A case is reported of a 37-year-old dock worker who was admitted with severe jaundice This was due to centrilobular hepatic necrosis caused by rheumatic heart failure The serum bilirubin level was 26 9 mg/100 ml, and to our knowledge such a high level has not been reported before Markedly increased serum-bilirubin values in patients with congestive heart failure should focus the attention on the diagnosis of centrilobular hepatic necrosis

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TABLE I Planimetric measurements of red cell and reticulocyte areas in 7 healthy males N = number of red cell — reticulocyte pairs measured Values are in arbitrary units

Sample	N	Mean red-cell area	Mean reticulocyte area	Ratio red-cell/ reticulocyte area
1	23	18 7	21 2	1 133
2	22	20 8	22 4	1 077
3	23	18 8	20 6	1 096
4	24	20 5	25 0	1 220
5	29	19 7	22 9	1 162
6	18	22 5	24 9	1 107
7	25	18 6	20 7	1 113
			Mean	1 130

Results

As shown in table I, the average area of normal reticulocytes is consistently larger than that of non-reticulated red cells On an average, the reticulocyte area was found to be 13 0 (range 7 7—22 0) per cent larger than the red-cell area Yet, occasionally reticulocytes were found which were smaller than adjacent non-reticulated red cells

As will be seen from the table there appears to be some inter sample variation in the mean red cell and reticulocyte areas In part, this variation may be due to slight differences in photographic enlargement from one sample to another However, the observed size differences between reticulocytes and red cells cannot be explained in this way because 1) within one sample, all enlargements were kept strictly uniform, and 2) red cells and reticulocytes were measured in pairs on the same glossy prints

Discussion

More than thirty years ago Wintrobe (31) demonstrated a temporary rise in erythrocyte mean corpuscular volume following specific therapy of pernicious anemia and showed that this increase was correlated with a high percentage of reticulocytes Similar observations have been made in phenylhydrazine-induced hemolytic anemia (1, 30) More recently, the sequence of events has been carefully studied and analyzed by Brecher and Stohlman (7, 8, 28) They observed that the reticulocytes formed in response to severe hemolysis, bleeding hypoxia, and erythropoietin stimulation are two to three times larger than the average red cell After the initial response to the erythropoietic stimulus has subsided the size-distribution curve of the red cells rapidly regresses toward normal In part this is due to production of smaller red cells Moreover, the originally formed large red cells have a short life span (28), which is consistent with earlier observations of a decreased red-cell survival time after severe bleeding (3, 19) Other possible mechanisms for the rapid restoration of normal red cell size would be shrinkage or division of reticulocytes Shrinkage has been ruled out on the grounds of the high hemoglobin concentration of the large reticulocytes (1, 7), and evidence for reticulocyte division (30) is lacking

The studies of Brecher and Stohlman (7 8 28) clearly demonstrate that the reticulocytes formed in response to severe stimuli are defective in terms of their survival time Although these large cells are useful as an immediate homeostatic mechanism, the final restoration of

red-cell mass rests with the production of smaller sized erythrocytes

This naturally leads to a reconsideration of the destiny of the normal reticulocyte Clearly, if the transition from reticulocyte to mature cell involves cell shrinkage and if normal reticulocytes had the same size as reticulocytes formed in response to severe stimuli i e about two to three times larger than an average red cell then the hemoglobin concentration of reticulocytes could not be more than about 1/2 to 1/3 of the hemoglobin concentration in the mature red cells Although some reticulocytes still synthesize hemoglobin (5 17), interference microscopy data indicate that the concentration of hemoglobin and in particular of protein (globin) in the later erythroblast stages is only slightly lower than in mature erythrocytes (16, 29) Consequently unless normal reticulocytes are much smaller than the reticulocytes formed in response to severe erythropoietic stimuli the common concept that the normal reticulocyte shrinks and matures to a normal red cell is untenable

So far attempts to concentrate reticulocytes from normal blood in order to directly measure their volume have been unsuccessful (8) The only available information on the size of normal reticulocytes *versus* that of red cells refers to their diameter in stained smears measured by means of an ocular micrometer (20 21) This method is of rather limited precision (2) and assumes that any change in nuclear diameter during preparation of the blood smear is equal in reticulocytes and red cells In the present study this difficulty was avoided by using wet preparations Moreover, any local changes in physicochemical conditions, e g distance between slide and coverslip, which might affect the absolute area of the cells, are not likely to change the ratio reticulocyte red-cell area because the cells were measured in pairs of one reticulocyte and one erythrocyte from the same field

According to the present data the *area* of normal reticulocytes is 13 per cent larger than that of average erythrocytes However to estimate reticulocyte volume, information about their shape and thickness is required It is believed that the shape of reticulocytes is similar to that of mature red cells (22) There is nothing to support the claim that reticulocytes are biconvex discs (30) Direct measurements of normal reticulocyte thickness are not available However, studies of the osmotic fragility of reticulocytes may shed light on the problem if it is accepted that osmotic fragility is an indicator of the diameter thickness ratio of the cell (9 12) Although species differences may exist (10, 11 13, 26), it is well established that in man, normal young red cells are more resistant than older cells (18, 23, 25) This suggests, although indirectly, that cell thickness relative to cell diameter, is no larger in reticulocytes than in mature red cells, and may actually be smaller Assuming as a rough approximation that reticulocytes and erythrocytes are simple sections of a column and that the diameter thickness ratio is equal in reticulocytes and older red cells, the volume of normal reticulocytes relative to that of older red cells can be estimated

With a ratio reticulocyte area : red-cell area of 1.13, the ratio reticulocyte radius : erythrocyte radius is $\sqrt{1.13}$, or about 1.065. If we assume a reticulocyte thickness : red-cell thickness ratio of 1.065, the ratio reticulocyte volume : red cell volume is $(1.065)^3$, or approximately 1.2. Thus, with these approximations and assumptions normal reticulocytes appear to be about 20 per cent larger by volume than non-reticulated red cells taken as a whole. This value is somewhat less than that calculable from measurements of reticulocyte diameters in smears (21). This excess volume of normal reticulocytes is very moderate compared with reticulocyte size during initial regeneration of red-cell mass (7, 30). It is apparent that the reticulocytes present in the blood during normal steady-state red-cell production are distinctly different from those emitted from the bone marrow in response to erythropoietic stimulation, as first considered by Ambs (1). Considerations of cell sizes (5) and of normal bone-marrow time and mass parameters suggest that normal reticulocytes are predominantly derived from orthochromatic normoblasts. The transit time of orthochromatic normoblasts in man is about 12—19 hours (4, 15). The ratio of orthochromatic normoblasts : reticulocytes in the marrow is about 1 : 2 (6, 14). If the orthochromatic normoblast were the sole source of reticulocytes and if all orthochromats became reticulocytes, the transit time of bone-marrow reticulocytes would be twice the orthochromatic transit time. Marrow reticulocyte transit time is estimated to be about 36 hours (6), compatible with the orthochromatic normoblast being the major source of normal reticulocytes. In contrast, there is ample direct evidence that the large reticulocytes found during early regeneration of red-cell mass are derived from earlier red-cell precursors, particularly polychromatic normoblasts, which have skipped one or more cell divisions (5, 24).

Summary

The areas of reticulocytes and erythrocytes were determined planimetrically in enlarged photomicrographs of bloods from seven normal males. The mean reticulocyte area was 13 per cent larger than mean erythrocyte area. With some assumptions the volume of normal reticulocytes is computed to be 20 per cent larger than the mean red cell volume. Thus, normal reticulocytes are considerably smaller than reticulocytes formed in response to severe erythropoietic stimuli.

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With a ratio reticulocyte area red-cell area of 1 13, the ratio reticulocyte radius erythrocyte radius is $\sqrt{1\ 13}$, or about 1 065 If we assume a reticulocyte thickness red cell thickness ratio of 1 065, the ratio reticulocyte volume red cell volume is $(1\ 065)^3$, or approximately 1 2 Thus, with these approximations and assumptions normal reticulocytes appear to be about 20 per cent larger by volume than non-reticulated red cells taken as a whole This value is somewhat less than that calculable from measurements of reticulocyte diameters in smears (21) This excess volume of normal reticulocytes is very moderate compared with reticulocyte size during initial regeneration of red-cell mass (7, 30) It is apparent that the reticulocytes present in the blood during normal steady-state red-cell production are distinctly different from those emitted from the bone marrow in response to erythropoietic stimulation, as first considered by Ambs (1) Considerations of cell sizes (5) and of normal bone-marrow time and mass parameters suggest that normal reticulocytes are predominantly derived from orthochromatic normoblasts The transit time of orthochromatic normoblasts in man is about 12—19 hours (4, 15) The ratio of orthochromatic normoblasts reticulocytes in the marrow is about 1 2 (6, 14) If the orthochromatic normoblast were the sole source of reticulocytes and if all orthochromats became reticulocytes, the transit time of bone-marrow reticulocytes would be twice the orthochromatic transit time Marrow reticulocyte transit time is estimated to be about 36 hours (6), compatible whith the orthochromatic normoblast being the major source of normal reticulocytes In contrast, there is ample direct evidence that the large reticulocytes found during early regeneration of red-cell mass are derived from earlier red-cell precursors, particularly polychromatic normoblasts, which have skipped one or more cell divisions (5, 24)

Summary

The areas of reticulocytes and erythrocytes were determined planimetrically in enlarged photomicrographs of bloods from seven normal males The mean reticulocyte area was 13 per cent larger than mean erythrocyte area With some assumptions the volume of normal reticulocytes is computed to be 20 per cent larger than the mean red-cell volume Thus, normal reticulocytes are considerably smaller than reticulocytes formed in response to severe erythropoietic stimuli

Acknowledgments

The assistance of the Division of Medical Photography Rigshospitalet is gratefully acknowledged

This investigation was supported by PHS Research grant CA 5492 HEM from the National Cancer Institute, U S Public Health Service

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With a ratio reticulocyte area : red-cell area of 1.13, the ratio reticulocyte radius : erythrocyte radius is $\sqrt{1.13}$, or about 1.065. If we assume a reticulocyte thickness : red cell thickness ratio of 1.065, the ratio reticulocyte volume : red-cell volume is $(1.065)^3$, or approximately 1.2. Thus, with these approximations and assumptions normal reticulocytes appear to be about 20 per cent larger by volume than non reticulated red cells taken as a whole. This value is somewhat less than that calculable from measurements of reticulocyte diameters in smears (21). This excess volume of normal reticulocytes is very moderate compared with reticulocyte size during initial regeneration of red cell mass (7, 30). It is apparent that the reticulocytes present in the blood during normal steady-state red-cell production are distinctly different from those emitted from the bone marrow in response to erythropoietic stimulation, as first considered by Ambs (1). Considerations of cell sizes (5) and of normal bone marrow time and mass parameters suggest that normal reticulocytes are predominantly derived from *orthochromatic* normoblasts. The transit time of orthochromatic normoblasts in *man* is about 12—19 hours (4, 15). The ratio of orthochromatic normoblasts : reticulocytes in the marrow is about 1 : 2 (6, 14). If the orthochromatic normoblast were the sole source of reticulocytes and if all orthochromats became reticulocytes, the transit time of bone-marrow reticulocytes would be twice the orthochromatic transit time. Marrow reticulocyte transit time is estimated to be about 36 hours (6), compatible with the orthochromatic normoblast being the major source of normal reticulocytes. In contrast, there is ample direct evidence that the large reticulocytes found during early regeneration of red-cell mass are derived from earlier red-cell precursors, particularly polychromatic normoblasts, which have skipped one or more cell divisions (5, 24).

Summary

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Myocardial Changes in Dystrophia Myotonica

By

G Arnason Th Berge and L Dahlberg

Dystrophia myotonica is a relatively rare disease (6, 8, 10) in which electro cardiographic changes suggestive of cardiac involvement have been describ ed Fisch (5), for example, reported such changes, usually prolonged P—R period, low rate and wide QRS, in 68 3 % of 85 cases Auricular fibrillation and flutter have also occasionally been reported (1 4, 5)

Up to 1958 Berthold (3) was able to trace only 45 cases in which necropsy had been done and in only 5 of them had histopathological changes been ob served in the myocardium The changes were described as fibrosis interstitial deposition of fat varying thickness of the fibres pathological forms of nuclei and nuclei rich in chromatin

Since histopathological changes were found in the heart at recent autopsy of 2 cases of dystrophia myotonica, a report of the changes was considered justified

Case reports

Case 1 A 45 year-old unmarried man without known heredity For the last 20 years before he died he had been receiving a disability pension because of muscular atrophy In 1957 he had been admitted to hospital because of cardiac incompensation bilateral pleural effusion and oedema of the legs Physical examination of the heart had revealed nothing abnormal Electrocardiography regular sinus rhythm 100/sec min PQ = 0 32 sec Successfully treated with aspiration and Diamox The picture of dystrophia myotonica was at that time fully developed with cataract myotonia muscular dystrophy with a typical electromyogram, and gonadal atrophy On that occasion liver cirrhosis of unknown origin was also detected On April 21, 1962 the patient was readmitted because of progressive cardiac incompensation He had then had resting dyspnoea severe oedema of the legs ascites and bilateral pleural effusion Heart slow auricular fibrillation No murmur Electrocardiography auricular fibrillation with low ventricular frequency, low voltage and isoelectric T waves Conventional treatment of incompensation was of no help

Abnormal laboratory values E S R 15—20 mm/1 hour Serum bilirubin 2 0 mg/100 ml Alkaline phosphatase 39 U Electrophoresis moderately increased concentration of gammaglobulins

Autopsy Large heart Slight concentric hypertrophy and dilatation of the right half of the heart The subepicardial fatty tissue was increased in amount and covered almost the entire surface of the heart The coronary

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Microscopically the myocardium showed slight interstitial fibrosis The muscle fibres nuclei and sarcoplasm were however, of essentially normal appearance In some areas however especially in the periphery the myocardium showed fatty infiltration (fig 3)

Discussion

Both cases of verified dystrophia myotonica had shown electrocardiographic abnormalities of the type previously described in this disease

The changes in the heart consisted of concentric hypertrophy dilatation of the right half, and an increased amount of subepicardial fatty tissue Microscopical examination revealed that large areas of the muscle had been replaced by connective tissue and fat In one of the cases severe changes were seen in the nuclei and the sarcoplasm Owing to anatomical differences the myocardium is not strictly comparable with skeletal muscle In dystrophia myotonica the nuclei in the skeletal muscle do not occupy a normal, peripheral position but are seen in the interior of the cell besides which the range of variation of the thickness of intermingled muscle fibres is wider than normal In the myocardium the nuclei normally occupy a central position and the muscle fibres always vary somewhat in thickness But the variation found in the present cases definitely exceeded the normal range and there was no hypertension coronary sclerosis or valvular lesions to explain the changes described Similar findings have also been found in other types of muscular dystrophy (11) Only in a few cases of dystrophia myotonica and in no case of myotonia congenita have such heart changes been reported

Various theories such as retarded acetylcholine mechanism (1) and disorders of the neurovegetative system (9) have been suggested to explain the electrocardiographic changes in dystrophia myotonica Measurement of the isometric relaxation phase in the left ventricle in myotonia (2), however, argues for an organic myocardial lesion in dystrophia myotonica but not in myotonia congenita

In the light of the various tentative hypotheses based on a supposed disorder of a neurochemical (humoral neuromyogenic) regulatory mechanism as the cause of the cardiac disorders (electrocardiographic abnormalities arrhythmia etc) in dystrophia myotonica, it was interesting to note that the two cases described had shown *not only* electrocardiographic abnormalities but also histological changes in the myocardium Furthermore, in *one* of the cases the microscopical picture of the myocardium resembled that of affected skeletal muscle in dystrophia myotonica, *i e* an abnormally wide range of variation of the thickness of the muscle fibres In view of these observations and of the absence of any known co existing disease to explain the changes it appears justified to question whether the electrocardiographic changes might not be due to cardiac lesions *i e* dystrophic involvement of the myocardium

Summary

Report of two cases of dystrophia myotonica showing electrocardiographic abnormalities and histological changes

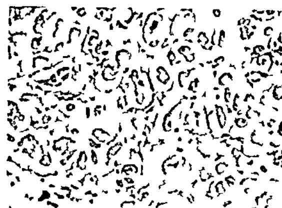
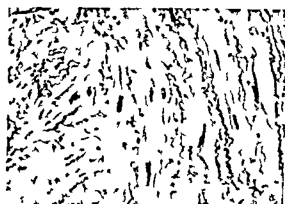


Fig 1 Transverse sect on of myocardium sho ving muscle f bres of vary ng th ckness (v G eson)



F g 3 Fatty infiltration of myocardium (v Gieson)



F g 2 Myocard al f bros s v ith spl tt ng of n uscle f bres and var at on n s ze of nuclei (v G eson)

vessels shov ed a fe atheromato is plaques but no luminal narro ng The valves and the orifices were of normal appearance

M croscop cally advanced interstit al f bros s v as seen with splitting (fragmentat on) of the mi scle fibres v hich varied idely in tl ck ness The nuclei d ffered markedly in sl ape and size and in some areas tl ey v ere rich in chromatin The sarcoplasm v as sometimes loose and vacuolated (f gs 1 and 2 (The liver shov ed typ cal s gns of portal cirrl os s)

Case 2 A 71 year old man v ho v as adm tted to the hosp tal in 1962 He had had verified dystroph a myotonica since 1948 He had tv o children both affected The patient v as 56 years at diagnosis of the disease v hich was then fully developed v ith cataract myotonia of the hands muscular dystrophy of the arms and legs and also impaired locomot on bradycard a and hypotension Neither electrocard ograph nor roentgen examination of the heart had been performed at that time The patient had been unable to work and the disease had cont nued to progress During the last 2 years of his l fe swallo ing diff cult es had super vened during the last 3—4 months before death he had been bedridden and during the last 14 days he had been febrile and disorientated v ith increas ng dyspnoea Heart no murmur Electrocard ography auricı lar fibrillation and some ventricular premature beats Roentgen exam nat on of the chest heart of normal size moderate pulmonary stas s (congest on) and right s ded bronchopneumonia (?)

The symptoms d d not respond to treat ment and the patient d ed from pulmonary oedema and bronchopneumon a a fev days after admiss on to hospital

Abnormal laboratory values E S R 49 mm 1 hour W B C 8 700—25 400 Hb 9 l g/ 100 ml R B C 3 5 mill

Autopsy Large heart Concentric hyper trophy and d latat on of the right ventricle The subepicard al fatty tissue v as increased and covered almost the entire surface of the heart The coronary vessels sho ed a fe atheromatous plaques but no narro ing of their lum na The valves and orifices v ere of normal appearance

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Summary

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in the myocardium In one of the cases the histological picture myocardium resembled that of affected skeletal muscle in this disease, i e an abnormally wide range of variation of thickness of the muscle fibres This suggests that the electrocardiographic abnormalities may be due to cardiac lesions, i e dystrophic involvement of the myocardium

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Epidemiological Study on Atherosclerosis in the Netherlands
(Supervisor F S P van Buchem), Haarlem The Netherlands

Hypertension and Changes of the Fundus Oculi

By

F S P van Buchem J W M Th v d Heuvel Aghina
and J E A v d Heuvel[1]

In general there exists unanimity of opinion that the examination of the fundus oculi is of great importance for the assessment of a patient with hypertension especially with regard to the prognosis

Although long ago in 1898 Gunn (10) already drew attention to these changes in the fundus there still exists much difference of opinion in several respects regarding the interpretation and evaluation of the changes found in hypertension This first of all is to be attributed to a difference in nomenclature (3) As Leishman (12) expressed it it was proved most difficult to translate the descriptive terminology derived from ophthalmoscopic studies into terms of basic pathology For example, a sufficient distinction was not always made between arteriosclerosis atherosclerosis and arteriolosclerosis At present it is generally accepted that the ophthalmoscopically visible retinal arteries are mainly arterioles (8, 16 17 20 22) Only the central retinal artery and the beginning of the first branches, where they have not left the papilla, are arteries In these atherosclerosis only can be expected to occur not in the arterioles, as believed e g by Sautter (16) Of greater significance is the type of arteriolosclerosis with intimal thickening and hyaline degeneration and narrowing of the vascular lumen to a greater or lesser degree

In atherosclerosis the changes, consisting of oedema, deposition of lipids, and neoformation of connective tissue, are mainly localised to the intima In arteriosclerosis the changes of the media are more prominent particularly degeneration of the muscle fibres and the elastic membranes — which are afterwards replaced by connective tissue — furthermore hyalinization and deposition of calcium Even though atherosclerosis and arteriosclerosis often occur

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TABLE II Ophthalmoscopic changes and blood pressure in males 40—60 years of age (changes of 'arteriolar sclerosis')

B P (mm Hg)	None	Wide light streak	Changes arteriovenous crossings	Copperwire art	Silver wire art	No
Systolic < 141 Diastolic < 91	213 (35 6%)	211 (35 3%)	152 (25 4%)	22 (3 7%)	—	598
Systolic > 140	42 (16%)	105 (40 6%	83 (32 1%)	26 (10%)	1	257
Diastolic > 90	18 (16 %)	43 (36 6%)	38 (34%)	14 (12 5%)	1	114
Systolic > 160 Diastolic > 110	2	3	6	5	1	17

height of the blood pressure or even the prognosis quo ad vitam from the condition of the retinal vessels

Scheie (17) remarks it embodies interpretations which are difficult for the average ophthalmologist and internist to use in everyday practice'

The need has arisen to separate fundal changes that are more closely connected with hypertension from those caused by arteriolosclerosis in which it is often assumed that this arteriolosclerosis is caused by the hypertension (17 20) Therefore Scheie has tried to make a distinction between the manifestations caused by a greater or lesser constriction of the arterioles in which the changes are still functional and the signs and symptoms due to arteriolosclerosis

As manifestations of the functional phase he indicates

Stage I Diffuse constriction of the arterioles more or less marked depending on the degree of the hypertension This may be absent in a mild *hypertension* but occurs especially in cases of rapidly evolving hypertension at an early age and in toxaemia of pregnancy

It has however been shown that only in young people does this fundal picture constitute an indication of *hypertension* (12 20) and that it may also develop as a result of obstruction of the central retinal artery that it is often found in people older than 50 (1) and even as a rule after the sixth decade as a result of organic vascular changes (12) in the absence of hypertension

In a population screening of men of the 40—60 age group (see below) we found with a systolic blood pressure less than 141 mm and diastolic less than 91 mm Hg a constriction of the arterioles in 6 2 % (table I)

Stage II Irregularity of the diameter of the arterioles considered by Scheie as due to local spasms but which can also be caused by *organic changes* (1 12, 15 21) because on *examinations repeated at long* intervals the constrictions are always found at the same site (21)

In the case of *spasm* the constrictions are more symmetrical (waistlike) and often variable (20) In elderly people especially the possibility of an organic cause should be taken into account and hypertension is not necessarily present (1)

Stage III In more serious forms of hypertension the marked spasm of the arterioles would *impede* the blood supply to the capillaries and tissues to such a degree that haemorrhages and exudates would occur

However these have also been attributed to necrotic and thrombotic changes of the arterioles which have been demonstrated

TABLE I Ophthalmoscopic changes and blood pressures (changes of ' hypertension) in males 40-60 years of age

B P (mm Hg)	None	Diffuse narrowing arterioles	Haemorrhages	No
Systolic < 141 Diastolic < 91	571	38 (6 2%)	—	609
Systolic 160—199 Diastolic 91 —109	31	6	1	38
Systolic > 160 Diastolic > 110	10	6	2	18

in combination, it is still wise to make an essential distinction between them

Keith et al (11) have introduced a classification of the fundus changes occurring in the different stages of hypertension They expected this classification to be especially useful for the prognosis

The following was their original classification

Stage I Slight narrowing or sclerosis of the retinal arterioles, hypertension causing no complaints and not disturbing general health

Stage II Moderate to marked arteriolosclerosis either of the chronic type, characterized by widened arterial reflex and arteriovenous compression, or of the post angiospastic type characterized by general and local irregular narrowing of the arterioles The hypertension is more marked and causes some complaints, *the general state of health* is good

Stage III Angiospastic retinitis characterized by oedema, exudates and retinal haemorrhages in a combination of sclerotic and spastic changes of the arterioles Blood pressure is often continuously high sometime there is a slight disturbance of cardiac and renal function The patients often suffer from nervousness *headache* giddiness nycturia, albuminuria and haematuria may be present

Stage IV Measurable papilloedema with the manifestations of stage III, as headache giddiness, loss of weight, nycturia Cardiac and renal function are disturbed at an earlier or later date, *serious condition* 79 % died within one year

Pickering (14) could not accept this classification, because, in this way the myth" is spread that local constrictions of the retinal arteries are usually caused by spasms Moreover no clear distinction is made between the benign and malignant types of retinopathy *The clinical* significance of a large, not sharply circumscribed exudate appearing in the fundus of a young man with a marked hypertension is quite different from the presence of a collection of sharply demarcated, glistening exudates in a 60-year-old man with a moderate hypertension while both of them would belong to stage III In the first case the nature of the exudate *and the circumstances* under which it appears suggest the early stages of hypertensive retinopathy and the beginning of the malignant phase of hypertension In the second case however the retinal picture is characteristic of the benign form of arteriosclerotic retinopathy

In Salus (15) opinion, even though there exists a certain parallel with the gravity of the affection, it is not possible to deduce the

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TABLE III

A Blood pressure groups

Systolic	Diastolic < 96	96—109	> 110
< 141	01	05	09
141—159	02	06	10
160—199	03	07	11
> 200	04	08	12

B Distribution of the retinal vascular changes in the different blood pressure groups

B P group	Arteriolosclerosis (retinal) 0	1	2	3	4	Esp [1]	Total no (men)
01	213	217	159	22	—	11	622
02	30	56	45	8	1	5	145
03	8	16	9	4	—	—	37
05	4	2	2	—	—	—	8
06	9	16	8	2	—	—	35
07	1	14	15	7	—	1	38
09	1	—	—	—	—	—	1
11	2	2	5	3	1	1	14
12	—	1	1	2	—	1	5
13	—	2	1	—	—	—	3
Total	268	326	245	48	2	19	08

[1] Cases without examination of the ocular fundus

C. Ocular fundus

0	No abnormality
1	Wide light streak
2	Changes arteriovein cross
3	Copperwire art
4	Silverwire art

histologically (1) In these cases of 'arteriosclerotic retinitis' the changes are often unilateral, accompanied by the crossing phenomenon but not by bilateral papilloedema The patients concerned are usually elderly people and the prognosis is better (14)

Stage II In this stage papilloedema is added to the other signs and symptoms

Manifestations pointing to arteriolosclerosis are, according to Scheie (17)

Stage I Widening of the arteriolar light reflex, which is said to be a result of the thickening of the wall

Biro (5), however, found out of 10,000 young people (between 15 and 30 years of age) examined for sporting purposes, a number having an elevated blood pressure with widened light reflex If, later on, the blood pressure fell the widened light reflex disappeared He therefore considers the widened light reflex no indication of arteriolosclerosis and Salus (15) found it not rarely in otherwise normal people

Vogelius et al (19) examined 124 elderly persons (40—95 years of age) with blood pressures below 140 mm systolic and 90 mm diastolic. The frequency of abnormal reflex increased with age

In a population screening of 908 males between 40 and 60 years of age, in which all social layers were represented (7), we found a widened light reflex in 211 of the 598 men with a systolic blood pressure lower than 141 mm and diastolic lower than 91 mm Hg (table II), it was not found in 40 of the 57 subjects with a systolic blood pressure higher than 159 mm and diastolic higher than 95 mm Hg (table III)

In view of the fluctuations in the blood pressure observed in many persons, we re-checked, after 1 and/or 2 years, the blood pressure in almost all men subjected to ophthalmological examination during the first investigation Tables IV and V only list the data of the men in whom the blood pressure had been recorded several times In the category shown with a blood

TABLE IV Distribution of the retinal vascular changes in the different age groups

	B P < 151/91				B P > 150/90				B P syst > 150 diast < 91			
	Age groups				Age groups				Age groups			
	40–44	45–49	50–54	55–60	40–44	45–49	50–54	55–60	40–44	45–49	50–54	55–60
Normal fundus	102 (55%)	73 (38%)	44 (25%)	9 (5%)	4 (31%)	8 (25%)	5 (12%)	3 (7%)	1	3	2	2
Widened light streak	52 (28%)	69 (36%)	75 (42%)	69 (41.8%)	5	12	9	19	1	2	1	9
Arterio-venous crossing phen.	25 (13%)	42 (22%)	53 (30%)	71 (43%)	2	11	17	14	—	1	1	5
Copperwire art.	3	4	3	13	2	2	8	9	—	—	2	2
Silverwire art.	—	—	—	—	—	—	1	—	—	—	—	—
Diffuse narrowing art.	7	13	10	9	1	4	4	5	—	—	—	1
Haemorrhages	—	—	—	—	—		3	—	—		—	—
Total	184	192	178	165	13	32	40	43	2	6	6	19

TABLE V Distribution of the vascular changes in different blood pressure groups

	B P		
	<151/91 (%)	>150/90 (%)	syst >150 diast <91 (%)
Normal fundus	31.7	15.6	24.2
Widened light streak	36.9	35.2	39.4
Arterio-venous crossing phen.	26.6	34.4	21.2
Copperwire art.	3.2	16.4	12.1
Other abnormalities	5.6	14.1	3.0
Total	719	128	33

pressure higher than 150/90 these values have therefore been found repeatedly. This demonstrates that the widened light reflex occurs just as frequently in the men with a systolic blood pressure lower than 151 mm and diastolic lower than 91 mm Hg as in the men with a blood pressure higher than those values (table V). Table IV gives the distribution of the retinal

TABLE III

A Blood pressure groups

Systolic	Diastolic < 96	96–109	> 110
< 141	01	05	09
141–159	02	06	10
160–199	03	07	11
> 200	04	08	12

B Distribution of the retinal vascular changes in the different blood pressure groups

B P group	Arteriolosclerosis (retinal) 0	1	2	3	4	Esp [1]	Total no (men)
01	213	217	159	22	—	11	622
02	30	56	45	8	1	5	145
03	8	16	9	4	—	—	37
05	4	2	2	—	—	—	8
06	9	16	8	2	—	—	35
07	1	14	15	7	—	1	38
09	1	—	—	—	—	—	1
11	2	2	5	3	1	1	14
12	—	1	1	2	—	1	5
13	—	2	1	—	—	—	3
Total	268	326	245	48	2	19	08

[1] Cases without examination of the ocular fundus

C Ocular fundus

0	No abnormality
1	Wide light streak
2	Changes arterioven cross
3	Copperwire art
4	Silverwire art

histologically (1) In these cases of 'arteriosclerotic retinitis' the changes are often unilateral, accompanied by the crossing phenomenon but not by bilateral papilloedema The patients concerned are usually elderly people and the prognosis is better (14)

Stage IV In this stage papilloedema is added to the other signs and symptoms

Manifestations pointing to arteriolosclerosis are, according to Scheie (17)

Stage I Widening of the arteriolar light reflex, which is said to be a result of the thickening of the wall

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In view of the fluctuations in the blood pressure observed in many persons, we re-checked, after 1 and/or 2 years, the blood pressure in almost all men subjected to ophthalmological examination during the first investigation Tables IV and V only list the data of the men in whom the blood pressure had been recorded several times In the category shown with a blood

TABLE IV Distribut on of the retinal vascular changes in the d fferent age groups

	B P < 151/91				B P > 150/90				B P syst > 150 diast. < 91			
	Age groups				Age groups				Age groups			
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W de l ght streak	52 (28°)	69 (36%)	75 (42%)	69 (41 8%)	5	12	9	19	1	2	1	9
Arterioven cross phen	25 (13%)	42 (22%)	53 (30%)	71 (43%)	2	11	17	14	—	1	1	5
Copperw re art.	3	4	3	13	2	2	8	9		—	2	2
S l erwire art	—	—	—	—	—	—	1	—		—		—
D ffuse narrowing art	7	13	10	9	1	4	4	5		—	—	1
Haemorrhages	—	—		—			3	—	—			—
Total	184	192	178	165	13	3?	40	43	2	6	6	19

TABLE V Distr but on of the vascular changes in d fferent blood pressure groups

	B P		
	<151 91 (%)	>150 90 %)	syst >150 diast 91 (%)
Normal fundus	31 7	15 6	24 2
W de l ght streak	36 9	3? 2	39 4
Arterioven cross phen	26 6	34 4	21 2
Copperw re art	3 2	16 4	12 1
O her abnormal t es	3 6	14 1	3 0
Total	719	128	33

pressure higher than 150 90 these values have therefore been found re peatedly *This* demonstrates that the widened light *reflex* occurs just as fre quently in *the men* with a systolic blood pressure lower than 151 mm and diastolic lower than 91 *mm Hg* as *in* the men with a blood pressure higher than those values (table V) Table IV gives the distribution of the *retinal*

vascular changes in the different age groups There is a definite correlation with age especially in the large group of men with a systolic blood pressure lower than 151 mm and diastolic lower than 91 mm The difference in frequency is statistically highly significant P < 0 0001 (Dr E F Drion) In the group with systolic blood pressure higher than 150 mm and diastolic higher than 90 mm the same difference is found but not so markedly (P = 0 07)

Based on these investigations, we may postulate that a widened light reflex usually has no relationship with the height of the blood pressure, but that it is a symptom of ageing Moreover, a widened light reflex occurs in affections of another nature, like, for example, a chorioretinitis disseminata and in allergic inflammations

Stage II Arteriovenous compression If of a light degree, this often occurs in combination with a widened light reflex, but in the case of heavier compression Scheie (17) speaks of stage II

Although arteriovenous compression is often regarded as an indication of arteriosclerosis (3, 15), Biro (4) in his above-mentioned investigation found that with the fall of blood pressure both the widened light reflex and the arteriovenous compression may disappear According to Salus (15) hypertension would always be present if the compression is accompanied by narrowing of the veins on both sides of the artery but this manifestation did not disappear with the fall of the blood pressure

Behrendt (3) found no correlation between the crossing phenomenon and hypertension It was often found to be absent in patients with a long and well corroborated history of hypertension , on the other hand marked crossing phenomena" did occur in people with normal blood pressure and even with hypotension

Seitz (18) applied in 100 cases the method that in one case had been applied by Leish man pathological examination of sites in the retina that had accurately been depicted shortly before death He found no relationship between the incidence of changes in intima and media of the arterioles and the degree to which Gunn s phenomenon had developed His conclusion is that this phenomenon can only be considered characteristic for the existence of a pathological proliferation of adventitia and glia at the site of crossing This proliferation certainly is found in hypertensives but may not as such be considered a characteristic of hypertension The apparent compression of the vein is an optical illusion, the vein preserves the same volume before, on and beyond the crossing Seits (18) recommends the use of red free light in addition to the normal white light in fundus examination In this way even a constriction caused by changes in intima or media can be distinguished from a spastic constriction The latter can, for example, be found in toxaemia of pregnancy and nephrogenic retinopathy

Biro (6) points out that on examination of a great number of young subjects, both during the lifting of a heavy weight by normal persons and in case of essential hypertension the crossing phenomenon was visible whilst no change of the vascular wall could be assumed, also according to Biro in elderly subjects the phenomenon suggests a change of the wall The patient s age should therefore be taken into consideration in the evaluation

In our above-mentioned investigation we found the crossing phenomenon in 152 of 598 males (40—60 years of age) with a systolic blood pressure lower than 141 mm and diastolic lower than 91 mm Hg, i e without hypertension (table II) Tables IV and V show that it is true, this phenomenon occurs more

TABLE VI The coincidence of the different retinal changes

	None	Diffuse narrowing art	Haemorrhages	Total No
None	256	12	—	268
Wide light streak	293	33	—	326
Arteriovenous cross changes	236	9	—	245
Copperwire art	39	7	2	48
Silverwire art	1	—	1	2
Total no	825	61	3	889

frequently in the men with a systolic blood pressure higher than 150 mm and diastolic higher than 90 mm than in normotensive men but here also a clear correlation with age is observed The crossing phenomenon occurs therefore frequently in the absence of hypertension (26 6 %) which would not be true if the vein is narrowed on both sides of the artery (15) According to table VI in only 9 of the 245 males with the crossing phenomenon a diffuse constriction of the arterioles was found

According to Schеie (17) *stage III* is characterized by the occurrence of copper wire arteries These first have been described by Gunn (10) in the following words their central light streak is very distinctive and sharp they have a metallic appearance Scheie (17) speaks of a burnished copper appearance

Most of the investigators regard the copperwire arteries as an indication of arteriolosclerosis (2 17) However hypertension is not rarely absent (9 22) for example in young diabetics (20)

Our study also showed that copper wire arteries are often found in the absence of hypertension viz in 22 of the 48 cases the systolic blood pressure was less than 141 mm and diastolic less than 96 mm Hg (table III) Table V demonstrates that these arteries occur more frequently with a higher blood pressure, but here also an influence of age is suggested (table IV) Table VI shows that in 39 of the 48 cases of copperwire arteries no retinal manifestations have been found that should, rather be considered as belonging to the hypertensive changes of the fundus (diffuse constriction of the arterioles, irregular diameter of the vessels, haemorrhages, exudates)

Stage IV In this stage so-called silverwire arteries are visible characterized by Ballantyne (1) as a metallic reflex seen in a narrow pale sclerosed artery Due to the extreme arteriosclerosis the column of blood becomes invisible, and the arterioles resemble white strands This phenomenon is generally considered an indication of a serious affection of the vascular wall

Salus (15) believes that "real silverwire and copperwire arteries are the only indications of a serious vasculopathy These silverwire arteries have also been observed without hypertension (1 20 22)

All this goes to show that many of the above mentioned fundal changes occur not rarely in the absence of hyper

tension This holds for the widened light reflex, the crossing phenomenon and the copperwire and silverwire arteries

In young subjects markedly narrowed arterioles suggest the existence of hypertension, which however is not true for people older than 60 years

Haemorrhages, exudates (especially the 'cottonwool" exudates) and papilloedema are particularly prone to occur in the more serious forms of hypertension, which develops rapidly, but they may disappear after adequate treatment In our population study we sometimes found retinal haemorrhages in men without any complaints, who were at work regularly, and whose blood pressure was not higher than 180/120 on repeated examination In one of these men the blood pressure later proved to be normal on repeated examination (the first time 170/110) Extensive general physical examination did not reveal any other abnormalities in these people

Marked crossing phenomena, copperwire arteries and silverwire arteries are therefore arguments in favour of the diagnosis of arteriolosclerosis

What is said above also proves that it is incorrect that arteriolar changes in the fundus are usually regarded as a result of hypertension In our population screening 275 of the 293 males with the crossing phenomenon or copperwire arteries, did not show any of the so-called functional hypertensive fundal changes (table VI), while 64 9 % and 45 8 % of the two groups, respectively had a systolic pressure less than 141 mm and diastolic less than 96 mm Hg

Apart from hypertension, there must therefore be still other causes giving rise to these phenomena, in which age proves to be a very important factor

Pickering (14) also points to the fact that in general hyaline intimal thickening of the smallest arteries increases in frequency and severity with age, and that, in this sense it can therefore be considered an ageing process in contrast to the acute fibrinoid arteriolar necrosis which is connected with a rapidly developing serious hypertension. This latter affection however, can not be verified ophthalmologically (20)

We also remark here that serious fundal changes with marked narrowing of the arterioles, haemorrhages, exudates and papilloedema not only occur in the malignant form of essential hyper tension, but also in hypertension caused by chronic glomerulonephritis, renal ischaemia, primary aldosteronism and phaeochromocytoma The blood pres sure need not always be particularly high in these grave retinal changes They have also been observed in only mild to moderate hypertension and even in the absence of hypertension (13) In the latter patients, it is true, hyper tension had been found previously, but without fundal changes

Finally, it is wise to realize that these serious fundal changes may be present 1) without hypertension (15, 21), and 2) with hypertension without the patients having complaints of any significance

A young man was referred to us because of hypertension found in a physical examina tion He was not under treatment and did his work regularly On ophthalmological examination he had markedly contracted arterioles and papilloedema Later on it

was shown that he had been drinking a considerable time and that he had to urinate frequently The examination revealed primary aldosteronism for which he underwent operation with success

Summary

Even though it is clear that ophthalmological changes are of great importance for the evaluation of a possible hypertension there is still much difference of opinion on the interpretation of those manifestations In a mass examination of 40—60 year-old men the eyes were also examined Based on these data, the current interpretations were tested The assumption that *manifestations* attributed to *arteriosclerosis (widened* light reflex arteriovenous crossing phenomenon copperwire arteries) are due to hypertension proved to be incorrect The widened light reflex was not related to hypertension, but depended especially on age Although the crossing phenomenon and copperwire arteries *occur more frequently in hypertension* they are in many cases present in subjects without hypertension and here also a correlation with age was found

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From the Municipal Hospital, Arnhem, The Netherlands

Jaundice with Conjugated Bilirubin in Hyperhaemolysis

By

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Current views describe hyperbilirubinaemia resulting from hyperhaemolysis as characterized by the exclusive presence of unconjugated bilirubin in the blood. This is *indeed* the case in moderate hyperhaemolysis. In the case of excessive hyperhaemolysis in adults, however, there may be considerable quantities *of conjugated bilirubin in the* blood associated with bilirubinuria, even while the liver is intact. Ignorance of this phenomenon can cause diagnostic *difficulties* and threatens to create confusion because liver damage is *erroneously* assumed as a cause of the jaundice.

Case reports

Case 1. A woman aged 57 was suffering from acquired acute haemolytic anaemia with auto-immune bodies. The total blood bilirubin concentration was 2.6 *mg/100 ml*, including 1 mg conjugated bilirubin *per* 100 ml. There was bilirubinuria. The liver *punc*tate showed normal features. SGOT 17 U, SGPT 11 U. Alkaline phosphatase 10.3 U (King Armstrong). Splenectomy was followed by *recovery*.

Case 2. A 37 year-old man developed arsenous hydride poisoning. The urine was the colour of port wine and besides a very large quantity *of urobilin* contained bilirubin. The blood serum contained methaemoglobin and oxyhaemoglobin. The total bilirubin concentration was 25 *mg/100 ml*. Conjugated bilirubin was demonstrable by column chromatography according to Cole et al. (4). The patient's clinical condition remained *good*. *On the* third day of illness column *chromatography* no longer revealed conjugated bilirubin *in the blood*. *The total* bilirubin concentration was normal on the 14th day.

Case 3. Similar data on conjugated bili*rubin in the blood* (demonstrated by column chromatography), associated with bilirubinuria, were obtained in another patient with arsenous hydride poisoning. This case, however, took a fatal course within two days. The macroscopy *and microscopy* of the liver were normal.

These observations suggested that *hyperhaemolysis* can give rise to jaundice with conjugated bilirubin *(in* addition to free bilirubin) while the liver remains intact. The first two of the above *examples, and* other observations have

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taught us that the jaundice disappears remarkably quickly once the haemolysis is arrested The patients in these cases are in excellent general condition, showing none of the features to be normally expected in the case of parenchymal liver damage

The salient point in the hyperhaemolysis with respect to jaundice, is an excessive supply of free bilirubin to the liver To explain the above findings, therefore, it seemed advisable to study how test animals and human subjects respond to intravenous administration of a large quantity of unconjugated bilirubin

Twenty two rabbits were given *100* or 150 mg bilirubin intravenously during 1 hour In blood obtained within 5 minutes to 3 3/4 hours of terminating the administration conjugated bilirubin was invariably demonstrated by column chromatography according to Cole et al (4) In three rabbits with a drain in the common bile duct submitted to intravenous administration of 100 mg bilirubin, 50 mg proved to be excreted with the bile within the first two hours In these animals, too, conjugated bilirubin was demonstrable in the blood (7)

We then started bilirubin tolerance tests in human subjects As early as 1959 Tisdale et al (9) gave five test subjects without hepatic anomaly 15 mg bilirubin/kg body weight over a period of 20—60 minutes using the method of Malloy and Evelyn on the basis of the one minute value they found a *concentration* of 0 7—2 29 mg/100 ml direct bilirubin These maximum concentrations were determined 1—2 hours after starting the test These authors also mentioned the occasional occurrence of bilirubinuria The direct bilirubin was *not further* identified as conjugated bilirubin

In personal human tolerance tests we made use of three non jaundiced patients (A B and C) with a drain in the biliary tract and without discernible disturbances in liver function After adequate recovery from surgery, these patients were given 600, 600 and 1,000 mg bilirubin (Homburg), respectively, by intravenous infusion within 30 minutes (8) The presence of *conjugated bilirubin* was qualitatively demonstrated by column chromatography The quantitative determination was carried out using the methods of Witmans et al (11) and of Weber and Schalm (10)

The results in these three patients were

Patient A Load *600 mg* Maximum blood concentration 45 minutes after starting the infusion 10 6 mg/100 ml including 3 mg/100 ml conjugated The total bilirubin concentration was already declining 15 minutes later (9 2 mg/100 ml), but showed a rise of the conjugated component to 4 5 mg/100 ml The jaundice had virtually disappeared 18 hours after starting the infusion Bilirubinuria became demonstrable 3 hours *after starting the infusion*

Patient B Load 1,000 mg Maximum blood concentration 1 hour after starting the infusion *19 3 mg/100 ml, of* which 3 4 mg/100 ml was conjugated The total bilirubin concentration after 3 hours had decreased to 11 7 mg/100 ml the conjugated component *of which* had risen to 6 3 mg/100 ml Only slight jaundice (total 2 3 mg/100 ml) remained 18 hours after starting the infusion Bilirubinuria was not examined

Patient C Load 600 mg Maximum blood concentration 1 hour after starting the infusion 7 9 mg/100 ml, of which

3 mg/100 ml was conjugated Hardly any jaundice (total 1 5 mg/100 ml) existed after 18 hours Bilirubinuria became demonstrable 3 hours after starting the infusion

Discussion

In each of these patients, an unmistakable increase in the conjugated bilirubin concentration of the bile (about 400 mg/100 ml) and a corresponding increase in the total excretion of conjugated bilirubin in the bile, was demonstrable throughout 6 hours after starting the infusion

Thus our experiments showed that, both in rabbit and in man a large intravenous load of bilirubin gave rise to jaundice in which a considerable proportion of the bilirubin (total 50 %) could be conjugated This was associated with bilirubinuria The intact liver proved capable of ensuring very rapid elimination of a large proportion of the bilirubin administered in high concentrations with the bile The jaundice was accordingly of short duration

A knowledge of this syndrome is of importance not only in haemolytic types of anaemia but equally in types of jaundice not completely understood In 1950 Caroli et al (3) described the ictères postopératoires non hémolytiques à bilirubine directe in patients who had undergone a gastrectomy and had received blood transfusion Cachin (2) described similar features as ictères pléiochromiques à bilirubine directe and ascribed them to administration of blood in which donor erythrocytes had become abnormally vulnerable as a result of too prolonged storage or other unfavourable storage conditions The bilirubin formed as a result of haemolysis, therefore, constitutes an additional bilirubin load Cachin s difficulty, however, remained to explain the finding of conjugated bilirubin when jaundice occurs

Pichlmayer and Stich (6) described eine neue Ikterusform beim Zusammentreffen von Operation, Narkose und Bluttransfusion' Within 7 months they collected 41 postoperative patients who showed this form of jaundice, characterized by its occurrence on the first postoperative day and its culmination on the 3rd—4th postoperative day The patient s general condition remained good there was no pruritus the faeces remained coloured There was direct hyperbilirubinaemia and bilirubinuria The liver function tests were undisturbed The occurrence of this form of jaundice was believed to correlate with the duration of the operation and the duration of storage of the blood transfused (usually three weeks) These authors assumed an obscure liver injury resulting from operation and anaesthesia, as a result of which conjugated bilirubin could not be adequately excreted

An explanation of the clinical findings of Caroli et al , Cachin and Pichlmayer & Stich presents itself on the basis of the experiments described which we carried out in test animals and human subjects with a normal liver This eliminates the theory of a disturbance in the excretory ability of the liver, as Pichlmayer and Stich developed In our experiments the excretion of conjugated bilirubin in the bile was unmistakably in

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Patient C Load 600 mg Maximum blood concentration 1 hour after starting the infusion 7 9 mg/100 ml, of which

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creased after administration of unconjugated bilirubin.

The type of jaundice described by these authors, therefore, shows the results of a bilirubin tolerance test with an intact liver. The stored blood administered — particularly if stored for some time — is the source of this bilirubin load. When completely haemolysed, 0.5 l blood certainly yields some 2,500 mg bilirubin. Transfusions of larger quantities of blood are common. Dependent on the duration of storage, an increasing proportion of the erythrocytes transfused fails to survive transfusion, and disappears from the recipient's circulation. Mollison (5) indicated that about 8 % of the erythrocytes of blood stored for 14 days, and about 24 % of those in blood stored for 28 days, disappears from the circulation within 24 hours of transfusion. In this process, a quantity of bilirubin can be liberated which is of the order of magnitude of the quantity used in our tolerance tests. The clinical picture, therefore, is not specific but merely constitutes an example of the excessive supply of bilirubin which can be seen in any form of hyperhaemolysis.

To explain the appearance of conjugated bilirubin in the blood in hyperhaemolysis, no parenchymal liver damage or disturbed bile elimination need be assumed. In these cases the characteristic feature, in fact, is the absence of manifestations indicative of such disturbances. Apart from this it has been demonstrated that, immediately upon administration of the load, a distinctly increased quantity of bilirubin is excreted in the bile. The most plausible view, at present, is in our opinion that the large quantity of unconjugated bilirubin offered is conjugated, but that this large quantity of conjugate, in spite of increased excretion, cannot be entirely excreted in the bile and consequently is diverted in part to the blood circulation. This is in accordance with experiments made by Arias et al. (1) in rats, which indicated that conjugation did not limit the overall metabolism of bilirubin. We believe that this presence of conjugated bilirubin is a consequence of overloading, particularly overloading of the excretory capacity of the otherwise normal liver.

Summary

Contrary to current views, very marked haemolysis can be accompanied by the presence of considerable quantities of conjugated bilirubin in the blood, and with bilirubinuria. This is based, not on liver damage per se — as demonstrated by bilirubin tolerance tests carried out in normal test animals and patients with an intact liver. The jaundice observed following transfusions of stored blood is merely an example of what is found in general in the presence of very marked haemolysis, regardless of its cause; it does not constitute a separate clinical entity.

A knowledge of this syndrome safeguards against errors in the differential diagnosis of jaundice.

Addendum

During the course of printing this paper the same syndrome was observed in a woman with a sudden large subcutaneous haematoma due to anticoagulant therapy. The normal unconjugated blood bilirubin (0.6 mg %) gradually rose in 7 days to 1.8 mg % total bilirubin of which 1 mg % was conjugated. Liver function tests were normal. On the 22nd posthaemorrhagic day the blood bilirubin had returned to 0.5 mg % without any conjugated bilirubin.

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Acta Medica Scandinavica Vol 176, fasc 5, 1964

From the Departments of Medicine (Head N Soderstrom, M D) and Clinical Chemistry (Head C G Holmberg M D) University Hospital Lund Sweden

A Diabetes Detection Campaign in Southern Sweden

Results of 69,000 Examinations

By

Lars Brandt Åke Nordén, Bengt Scherstén and Nils Tryding

Extensive studies of the frequency of diabetes are being carried out in various parts of the world Even though no agreement has been reached about the ideal test to be used or how to evaluate the data collected it appears to be of interest to obtain some information about the occurrence in different populations There seems to be no reason why diabetes should be equally common everywhere For the planning of health service schemes each country has to make its own inventory

In 1962 a campaign was launched intended to cover the 350 000 inhabitants of Malmohus lan representing one of the two Southernmost counties of Sweden During the first year 68 972 persons have been tested representing an 82 4 per cent response of the population over 15 years of age We hope to collect information about the remaining 17 6 per cent but so far this has not been possible The number of known diabetics comprised 0 96 per cent in this portion of the population The number of previously unknown cases of diabetes requiring treatment which were discovered during the campaign amounted to 0 35 per cent An intermediate suspect group added another 0 21 per cent, giving a total percentage of 1 5 in the group subjected to the tests

Material and methods

The tests were performed in connection with miniature X ray examinations of the chest The population was informed through local meetings and brochures For the tests a urinary sample was collected 2—4 hours after a meal rich in carbohydrates and tested with clinistix (Ames Co) In addition everybody was asked to fill in a questionnaire on the cards used for the X ray examinations. Thus information about previously known diabetes and the presence of diabetes in the family was collected

Those showing a positive clinistix were summoned at a later date for an oral glucose tolerance test at a special laboratory set up in the University Hospital in Lund The positive reactors were asked to include bread

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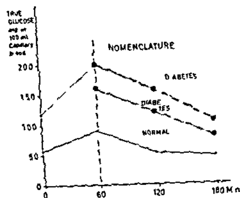


Fig 1 Glucose tolerance test 30 g glucose per m² of body surface orally

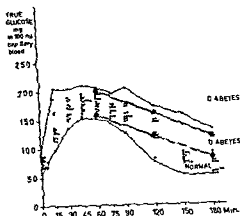


Fig 3 Glucose tolerance test Diabetic³ response in 20 persons Further checking required.

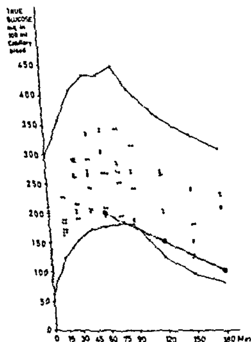


Fig 2 Glucose tolerance tests. Diabetic response in 0 persons 40 – 0 years old

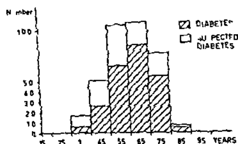


Fig 4 Newly discovered cases of diabetes and of suspected diabetes.

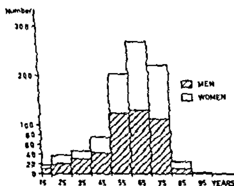


Fig 5 Age and sex distribution of diabetes (known and newly discovered cases)

TABLE I Diagnostic criteria

Diagnosis	Capillary blood glucose mg/100 ml after (min) 30	60	120	180
Diabetes	–	>200	>155	>105
Diabetes?	–	160–200	120–155	85–105
Oxyhyperglycemia	>180	<160	<120	<85
Renal glycosuria	–	<160	<120	<85

in every meal for three consecutive days preceding the glucose tolerance test It was checked that this instruction was followed The participants arrived fasting and were given an oral dose of 30 g glucose per m² of body surface as suggested by Klimt et al (6) They rested comfortably on a couch during the three hours of the test except only for the movements necessary for delivering urinary samples after 60, 120 and 180 minutes Samples of capillary blood were taken fasting and after 15, 30, 45, 60 75, 90 120 150 and 180 minutes Blood glucose concentration was determined by the glucose oxidase method according to Marks (9) as modified by Laurell (7) The urine was tested with clinistix The examination also included a physical overhaul and ophthalmoscopy without dilatation of the pupils

The diagnostic criteria are given in table I and fig 1

Cases with positive clinistix tests in the urinary samples collected during the glucose tolerance test with a normal blood glucose curve were labelled as renal glycosuria Glycosuria in samples of urine collected during fasting was not required for the diagnosis of renal glycosuria

When the present studies already were underway, some remarkably low fasting blood sugar values were observed In the technique employed the blood samples were collected during the three hours of the glucose tolerance test and then analyzed simultaneously During this period a decrease in the glucose content of the samples was found to take place amounting to between 10 and 20 mg/100 ml during three hours In each series the first part of the curve is therefore correspondingly lower Recently all samples have been kept at + 4° C which practically eliminates the changes in glucose concentration Re-evaluation of the data by introducing a correction factor has been made For the results this has had only minor consequences as the values recorded at 60 minutes and later formed the main basis for the diagnosis A few cases labelled as normal should be regarded as "diabetes?" and some "diabetes?" should belong to the true diabetic group, some cases of renal glycosuria should perhaps belong to the "diabetes?" group

Results

In 661 instances or 0 96 per cent of the 68,972 individuals taking part in the examination, reports were obtained about already known cases of diabetes A positive clinistix test was recorded in 620 cases not previously suspected of suffering from diabetes (0 90 %) Glucose tolerance tests were performed on 595 persons, while 25 did not appear for further examination

Diabetes unquestionably requiring treatment was found in 242 cases (0 35 %) Fig 2 illustrates the glucose tolerance curves obtained in 20 consecutive cases in the 40 to 50 year age group It seems remarkable that even in this age group there were people who had had no symptoms or only such vague feelings of discomfort that they had not spontaneously sought medical advice After closer questioning some admitted that they had been slightly more thirsty than usual In

the group of 242 cases with newly dis covered diabetes 14 cases of diabetic retinopathy were found In two instances gangrene of a toe was discovered One of these had been treated a month earlier at a hospital without the diabetes being diagnosed, the other had not previously been recognized In this group 57 patients reported that diabetes had occurred in the family (23 5 %)

"Diabetes?" was found in 142 instan ces (0 21 %) Typical glucose tolerance curves are presented in fig 3 According to the criteria of Conn (2) these persons were actually diabetic but it was felt that they could be kept under observation and submitted to a new test after a suitable in- terval No treatment was instituted That this group is close to the diabetic group is suggested by the report in 22 5% of the cases that diabetes had occurred in the family The entire material gave this in formation in 5 4 %

The age distribution of the newly dis- covered cases of "diabetes and dia betes?" is illustrated by fig 4 Cases were disclosed even in the 30-to-40 year group but the majority appeared in the 50 to 60-to-70 year age groups The rapid rise at 50 years was not due to a domination of female diabetics as is seen from fig 5 which also includes the already known cases of diabetes The rise in the fre quency of diabetes with increasing age is seen from fig 6

Renal glycosuria was found using the criteria already mentioned in 149 cases or 0 22 % The results of tests in 20 per sons are summarized in fig 7 Renal glyco- suria was not found to increase with ad vancing age it may diminish slightly fig 8 Renal glycosuria was predominantly

TABLE II Summary of findings

	No of cases	%
Diabetes already known	661	0 96
Diabetes not previously known	242	0 35
Diabetes?	142	0 21
Renal glycosuria	149	0 22
Oxyhyperglycemia	20	0 03
Not diabetes	42	0 06
Not appearing for glucose tolerance test	25	0 04
Total no taking part	68 972	100 00

found among men, as is seen from fig 9 There were 20 women and of them 8 were known to be pregnant — which might reduce the number of women belonging to the group of renal glyco- suria In the group with renal glycosuria information about diabetes in the family was obtained in 15 % of the cases So far, however, we do not know whether the relatives had renal glycosuria or true diabetes

Oxyhyperglycemia ("oxy from Greek oxus = sharp) appeared in 20 persons, 10 of whom had been operated on be cause of gastric ulcer An additional two had had gastric ulcer but had not been operated The typical response in this group is illustrated by fig 10

Discussion

The present search for previously un- known cases of diabetes has given the results summarized in table II By and large they are in agreement with similar reports (table III) Earlier studies from the Scandinavian countries have recently been summarized by Jorde (5)

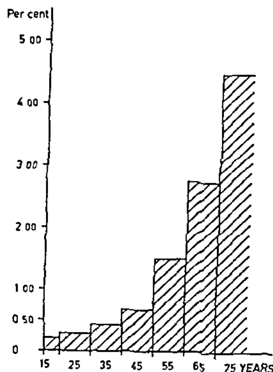


Fig 6 Cases of diabetes as a percentage of the number of persons examined Age distribution

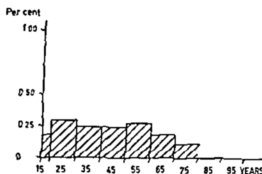


Fig 8 Cases of renal glycosuria as a percentage of the number of persons examined Age distribution

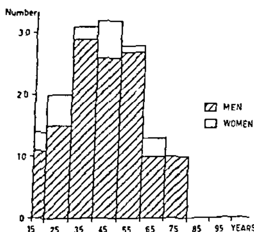


Fig 9 Age and sex distribution of renal glycosuria

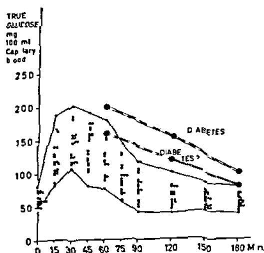


Fig 7 Glucose tolerance tests Renal glucosuria Twenty persons 40—50 years old

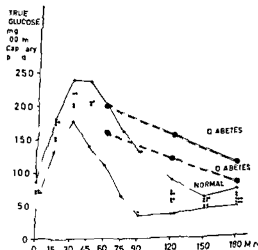


Fig 10 Glucose tolerance tests Oxyhyper glycemic reponse in 10 persons earlier subjected to gastric resection

cases of diabetes reported that the disease was already known to occur in the family which is in accordance with general experience (8). Our group "Diabetes?" had a family incidence of 22.5 %. The figure given by the entire 68 972 was 5.4 %. The number of cases with renal glycosuria agrees with Scherstén's (10) report of 0.28 %. In 42 instances no signs of diabetes or any other disturbance of the glucose tolerance were discovered. This group must have been due to false positive reactions in the original urinary test.

Summary

In a diabetes detection survey in the Southern part of Sweden 82.4 per cent of the population over 10 years of age or 68 972 persons were examined by urinary clinistix tests. Information about already known diabetes was obtained from 661 persons (0.95 %). In 620 instances a positive clinistix was recorded. 595 persons were further studied by a 3 hour oral glucose tolerance test and 242 cases of florid diabetes were found (0.35 %), 142 labelled "diabetes?" (0.21 %), 149 as renal glycosuria (0.22 %), 20 as oxyhyperglycemia (0.03 %), while 42 showed a normal test and were presumably pseudopositive in the original clinistix test (0.06 %).

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TABLE III Some published reports on frequency of diabetes using different methods

Author	Region	No	Age groups (yrs)	Method: Questionnaire	Method: Urine	Method: Blood	Percentage with diabetes
Dahlberg et al. (3)	Sweden	–	–	+	–	–	0 35
Silwer & Oscarsson (11)	Kristianstad lan Sweden	–	–	+	–	–	0 46 0 57
Walker & Kerridge (13)	Ibstock England	4 105	> 5	–	+	–	1 39
Schersten (10)	Blekinge Sweden	100 000	>10	–	+	–	1 7
Wilkerson & Krall (14)	Oxford Mass USA	3 516	–	–	+	+	2 0
Jorde (5)	Bergen Norway	5 930	>14	–	+	+	1 62–1 77
Tabor & Frankhauser (12)	Ottawa Canada	550	>40	–	+	+	4 0
Chesrow & Bleyler (1)	Oak Forrest Ill USA	1 000	>60	–	+	+	6 4

The number of cases found depends on the method used for screening and the fraction of the population appearing for examination If blood samples are included in the screening a much greater number of cases in the older age groups will of course be found The 242 cases of florid diabetes in the present series picked up by a positive clinistix test when urine had been collected after a meal rich in carbohydrates showed a negative urinary clinistix in 76 cases when reporting back fasting for the glucose tolerance test Had fasting urinary samples been used for the screening one third of the cases with florid diabetes would have been missed

The present study gives an incomplete picture of the frequency of diabetes in the region as no information is available concerning the 17 6 % not taking part in the survey The percentage figures refer to those examined With this reservation the newly discovered cases of florid diabetes represented 0 35 % An intermediate group labelled diabetes? formed another 0 21 % They probably also belong to the group of true diabetics As no blood glucose determinations were included in the screening only the more advanced cases have been spotted The figure of 1 5 % must be regarded as too low and not representative of the frequency of diabetes in Malmohus lan In a study of 100 000 persons carried out in a similar way in the neighbouring county of Blekinge Schersten (10) arrived at a figure of 1 7 % Walker and Kerridge (13) attempted to track down all the diabetics among the 4 105 inhabitants of Ibstock in England A figure of 1 39 % was found Jorde (5) examined urinary samples and capillary blood from 5 930 inhabitants in Bergen and found a diabetes prevalence of 1 62 % for men and 1 77 % for women

In the present study 23 5 % of the members of the group of newly discovered

cases of diabetes reported that the disease was already known to occur in the family, which is in accordance with general experience (8) Our group "Diabetes?" had a family incidence of 22 5 % The figure given by the entire 68,972 was 5 4 % The number of cases with renal glycosuria agrees with Scherstén's (10) report of 0 28 % In 42 instances no signs of diabetes or any other disturbance of the glucose tolerance were discovered This group must have been due to false positive reactions in the original urinary test

Summary

In a diabetes detection survey in the Southern part of Sweden 82 4 per cent of the population over 10 years of age or 68 972 persons were examined by urinary clinistix tests Information about already known diabetes was obtained from 661 persons (0 95 %) In 620 instances a positive clinistix was recorded 595 persons were further studied by a 3 hour oral glucose tolerance test and 242 cases of florid diabetes were found (0 35 %) 142 labelled diabetes?" (0 21 %), 149 as renal glycosuria (0 22 %) 20 as oxyhyperglycemia (0 03 %) while 42 showed a normal test and were presumably pseudopositive in the original clinistix test 0 06 %)

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From the Second Medical Clinic Sahlgrenska Sjukhuset University of Gothenburg
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A Double Blind Study of Dicumarol Prophylaxis in Coronary Heart Disease

By

G Aspenström and K Korsan Bengtsen

This is the final report of a trial started in 1956 and earlier in some details presented at the 27th Scandinavian Congress of Internal Medicine in 1960 (1) The study was planned with a double blind technic partly because that might give us a chance to evaluate any effect on anginal pain Such an effect we had previously found to be probable after several months of treatment (2)

Material and methods

From March 1956 until August 1958 all patients admitted to the Sec Med Clin for myocardial infarctions angina pectoris or atherosclerotic heart disease (without hypertensive or valvular disease) were included in the study if they did not show any definite contraindications Age in itself was not regarded as a contraindication

At the end of their hospital stay during which they were all on dicumarol the patients were classed according to type of disease age sex and risk group For the risk grouping the criteria of Russek et al (12) were used This initial subgrouping was made to compensate for the relatively small number of patients expected especially of women The patients having odd numbers within any subgroup then were given dicumarol tablets when discharged from the hospital, even numbers were given placebo tablets

For the purpose of the experiment the authors were the only two who knew to which series any patient belonged In the out patient control the other physicians of the clinic took care of the patients but had nothing to do with their dicumarol dosage and usually not with any hemorrhagic complication which was to be reported to us only For the last two years this double blind technic has been abandoned as the few remaining patients were too well known to all the doctors No patient however is aware of the experimental character of their treatment In the last year the remaining placebo patients have been successively given small doses of dicumarol instead of their placebo tablets without any effect on the blood values This has been done to make possible a change over to effective dicumarol dosage in those placebo patients in whom we may find it indicated when the study is now ended December 1963)

When admitted to hospital because of any disease needing strict immobilization, 31 placebo patients have been given dicumarol

Submitted for publication March 16 1964

TABLE I Types of heart disease and risk grouping

	Sex	Dicumarol series No	Dicumarol series Average age	Placebo series No	Placebo series Average age
Type of heart disease					
Infarctions	♂	60	62 9	60	61 8
	♀	28	63 4	31	66 0
Angina only	♂	5	59 9	5	59 5
	♀	9	68 6	6	67 6
"Cardiosclerosis"	♂	11	64 5	6	65 3
	♀	5	65 8	5	63 0
Total		118	63 6	113	63 4
Risk groups					
Good	♂	24	59 7	24	59 0
	♀	16	65 3	9	60 9
Poor	♂	52	63 2	47	63 5
	♀	26	67 1	33	67 2

TABLE II Age groups and final outcome

Age at start in the study	Dicumarol series Still living	With drawn	Dead	Total	Placebo series Still living	With-drawn	Dead	Total
−39	—	—	—	—	—	—	1	1
40−49	—	1	—	1	3	—	1	4
50−59	18	11	12	41	17	4	11	32
60−69	21	12	17	50	21	6	23	50
70−79	3	13	10	26	4	8	11	23
80−	—	—	—	—	—	—	3	3
Total	42	37	39	118	45	18	50	113
Average age	61 4	64 1	65 5	63 6	60 5	67 3	64 9	63 4

temporarily for a total period of 36 months as a prophylaxis against venous thrombosis

Dicumarol was used throughout the study and was put to our disposal by the Swedish manufacturer (AB Ferrosan) together with placebo tablets of identical appearance and taste

The anticoagulant effect has been controlled by the PP method of Owren PP levels of 10—25 % have been the aim In the

TABLE III Observations months

		Dicumarol series[1]				Placebo series[2]			
		Good risk		Poor risk		Good risk		Poor risk	
	Sex	No	Months	No	Months	No	Months	No	Months
Patients living or withdrawn	♂	20	1 233	28	1 461	20	1 427	19	1 315
	♀	15	838	16	811	8	563	16	863
Patients dead during observ period	♂	4	211	24	385	4	171	28	691
	♀	1	19	10	247	1	27	17	453
Total		40	2 301	78	2 904	33	2 188	80	3 322

[1] Whole series 118 with 5 205 obs months average 44 months

[2] Whole series 113 with 5 510 obs months average 49 months

placebo patients the intervals and the dosage have been changed in about the same way as in dicumarol patients

The dicumarol and placebo series initially did not differ significantly with regard to heredity previous infarctions thromboembolism blood pressure blood lipids heart volume congestive failure or rhythm disturbances.

The initial number of patients in the dicumarol series was 118 with 76 men and 42 women and in the placebo series 113 with 71 men and 42 women Their types of heart disease and the risk grouping appear from table I The age groups and the final outcome of the patients in each of them are presented in table II

Already in 1960 it was evident that in this material age in itself was no factor of decisive importance (1) The important point is that poor risk patients dominate the older age groups Any division of this material at 55 or 60 years of age is meaningless and gives no further information than does the division into good and poor risk groups

The number of observation months in total and in some subgroups is shown in table III

During the almost 8 years the study has lasted 37 patients have had to be withdrawn from the dicumarol series and 18 from the placebo series The causes are recorded in table IV Their later fate has been followed for at least two years and table V will show the deaths occurring after withdrawal

Results

Mortality

The number of deaths in the trial and the mode of death can be seen from table VI Sudden death is the most common type In no one of the patients in whom autopsy was performed could an instantaneous death be shown to be due to a recent coronary thrombosis It is worth mentioning that of the 33 autopsies in the placebo series 6 showed mural heart thrombosis but none in the dicumarol series

In any material of patients with an average age of 64 years at the start, the natural mortality tends to obscure differences caused by the therapy and the more so the longer the study is extended The crude mortality is not significantly

TABLE IV Cause of withdrawal (in some patients more than one cause)

	Dicum	Plac
Bleeding complications	12	[1]2
Admitted to other hospital (geriatric service)	8	10
Senility and/or lack of cooperation	6	8
Hypertension	4	2
Not willing to continue	4	2
Cancer	4	—
Leukemia	1	—
Sidero-achrestic anemia	1	—
Renal insufficiency	1	—
Alcohol abuse	1	—
Attempted suicide with placebo tablets	—	1

[1] One patient with hepatic cirrhosis and bleeding tendency One patient with several large and ultimately fatal gastrointestinal bleedings from unknown source

TABLE V Cause of death in patients previously withdrawn from the series

	No	Time after withdrawal
Dicumarol series		
Sudden death	8	3 months to 2 years
Myocard insufficiency	2	1 and 4 months
Cerebral infarction	1	2 years
Re infarction and cerebral embolism	1	9 months
Re infarction and lung cancer	1	6 months
Uremia	1	6 months
Hypernephroma	1	6 months
Leukemia	1	2 months
Total	16	
Placebo series		
Sudden death	1	4 years
Cerebral hemorrhage	1	1 year
Bowel perforation	1	2 months
Gastrointestinal bleeding	1	2 months
Total	4	

lower in the dicumarol series but the numbers of fatal infarctions show a difference, significant at the 5 % level The only striking difference is here to be found between the good and poor risk patients The annual mortality of these groups is recorded in table VII and the survival rates in fig 1

The high mortality in the dicumarol series during the first year was caused by a large number of sudden deaths occurring in male patients during the first six months

At the end of the fifth year, deaths and withdrawals had reduced the number of good risk dicumarol patients from 40 to 23 with 5 deaths (12 5 %),
poor risk dicumarol patients from 78 to 24 with 33 deaths (42 %),
good risk placebo patients from 33 to 28 with 3 deaths (10 %),
poor risk placebo patients from 80 to 26 with 43 deaths (54 %)

The 5 year survival rates, calculated from average number of participants and number of deaths during each year, are
for good risk patients on dicumarol 0 84,
for poor risk patients on dicumarol 0 47,
for good risk patients on placebo 0 91,
for poor risk patients on placebo 0 34

The difference in 5 year survival between the poor risk groups is not statistically significant because of the large number of sudden deaths among dicumarol patients during the first

TABLE VI Deaths during treatment or observation period

Dicumarol series	Autopsy		Autopsy		Placebo series
	Yes	No	Yes	No	
Sudden death	9	13	10	14	Sudden death
Myocard infarction	*5	—	14	—	Myocard infarction
Cerebral hemorrhage	5	—	1	1	Cerebral hemorrhage
Cerebral infarction	1	—	3	1	Cerebral infarction
Pulmonary embolism	*1	—	1	—	Pulmonary embolism
Gastrointest bleeding	1	—	1	1	Gastrointest bleeding
Chron. myocard insuff	2	—	1	—	Rupture of aortic aneurysm
Acute myocard insuff	1	—	1	—	Uremia
Pneumonia	1		1		Cancer
Total	*26	13	*33	17	

P = 0 05

* Two weeks after severe bleeding and multiple transfusions PP level 80—100%

* Mural thrombosis in none

* Mural thrombosis in 6 cases

TABLE VII Annual mortality Deaths No of patients at the beginning of each year

	Dicumarol series				Placebo series			
	Good risk		Poor risk		Good risk		Poor risk	
Year	No	%	No	%	No	%	No	%
1	0 40	0	19 78	24	1 33	3	12/80	15
	1 35	3	4 50	6	1 32	3	10 64	16
3	0 31	0	4 41	10	1 31	3	11/53	21
4	1 30	3	5 36	14	0 29	0	6 40	1[illegible]
5	3 29	10	1 27	4	0 28	0	4 32	12 5
6	0 23	0	0 [illegible]4	0	0 28	0	2 26	8
7	0 23	0	1 22	4 5	2 26	8	0 2[illegible]	0
8	0 22	0	0 21	0	0 24	0	0/21	0

year Through second to fifth years however the difference in mortality between the two poor risk groups is almost significant (0 05 > P > 0 02)

Myocardial infarctions

The prophylactic effect of anticoagulants on myocardial infarction is somewhat difficult to evaluate because it is impossible

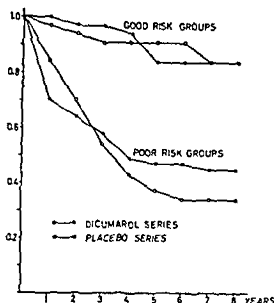


Fig 1 Survival rates calculated in the following manner (6)
a = total number on treatment at the beginning of the year,

$b = a - \frac{\text{number of withdrawals during the year}}{2}$,

c = number of deaths during the year,

$d = \frac{c \times 100}{b}$,

e = d × f (of preceding year)
f = survival rate at the end of the year = 1 00 — Σe

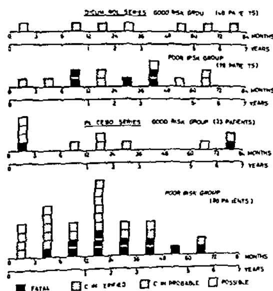


Fig 2 Time for and type of myocardial infarctions

to calculate, even approximately, the number of non-fatal infarctions with cause other than acute coronary thrombosis Also, a recurrent infarction in patients with a previous infarction and/or a pathological ECG is difficult to diagnose In several cases, readmitted to the hospital, no definite diagnosis has *been possible These patients have been* classified as having probable or possible infarctions Including them, the number of infarction episodes has been

in 40 good risk patients on dicumarol 7 during 2,301 observation months,
in 78 poor risk patients on dicumarol 13 during 2,904 observation months,
in 33 good risk patients on placebo 11 during 2,188 observation months,
in 80 poor risk patients on placebo 34 during 3,322 observation months

The difference between the two poor risk groups is significant, the frequency of infarction per thousand observation months being 4 5 and 10 respectively Also the difference between the two entire series *is significant,* 3 8 per thousand months as against 8 2

Fig 2 illustrates the distribution of the infarction episodes In this and in the following figures the first year has been split up to show the presence or absence of any "rebound phenomenon" in the placebo series in which the anticoagulant therapy was abruptly withdrawn at the start of the study

Thromboembolism

An effective anticoagulant therapy should almost completely abolish venous thrombosis and reduce arterial embolism very substantially

In the dicumarol series the following thromboembolic complications have occurred (myocardial infarctions and unclassified cerebrovascular incidients excluded)

Good risk group One male patient with retinal vein thrombosis after 77 months PP value 15—20 %

Poor risk group One male patient with venous thrombosis after 20 and 27 months PP value > 50 %

One male patient with fatal pulmonary embolism after severe bleeding at 24 months PP value 80—100 % since 2 weeks

One female patient with thrombophlebitis after 33 months PP value 20 %

In the placebo series the thromboembolic complications have been

Good risk group One male patient with thrombosis and pulmonary embolism after 13 months and another fatal pulmonary embolism after 16 months

Poor risk group Twenty episodes in male and seven in female patients See fig 3

These figures make it clear that in good risk patients thromboembolic complications have been so rare that anticoagulant therapy would have made no difference to them For poor risk patients the difference is highly significant

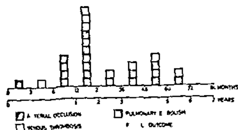


Fig 3 Time for and type of thromboembolic episodes in poor risk placebo patients

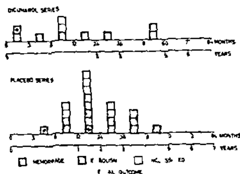


Fig 4 Time for and type of cerebrovascular incidents

Cerebrovascular incidents

Anticoagulants are dangerous in old patients with vascular disease and in hypertension because of the risk of cerebral hemorrhage On the other side cerebral embolism is a common complication after myocardial infarction with damage to the endocardium and in auricular fibrillation With a proper selection and anti hypertensive therapy the gain these patients can get from anticoagulants will probably outweigh the risk From fig 4 it can be seen that the acute mortality from cerebrovascular disease is about the same in the two series but that cerebral embolism has been a real threat to the placebo patients No embolism and only two possible cerebral infarctions (or small hemorrhages) have occurred in the dicumarol series All episodes with a verified or probable embolic cause have occurred in poor risk patients

Hospital treatment

In 1960 when reviewing the results in patients with myocardial infarction after an average observation time of 27

TABLE VIII Number of hospital months per thousand observation months in good and poor risk groups

	Sex	Dicumarol Good	Dicumarol Poor	Placebo Good	Placebo Poor
Living and	♂	7	10	4	4 5
withdrawn	♀	8	18	3	32
Dead	♂	6	15 5	4	52
	♀	—	63	74	57
Total		7 25	[1]17 5	4 75	[1]29

[1] P = 0 05

TABLE IX Anginal pain at end of second year in the study

	Sex	Accentuated	Unchanged	Diminished	Total
Dicumarol	♂	12	6	19	37
series	♀	7	8	11	26
Total		19	14	[1]30	63
Placebo	♂	13	13	9	35
series	♀	4	8	7	19
Total		17	21	[1]16	54

[1] P ~ 0 05

months, we found the time of hospital treatment because of cardiovascular disease or bleeding to be significantly longer for placebo patients The number of hospital months per thousand observation months was then 15 months in the dicumarol series and 30 in the placebo series of myocardial infarctions (1)

At the end of the study we have now included the groups of angina pectoris and cardiosclerosis We have split the figures to get the risk groups separately The result is presented in table VIII The difference is now reduced to be significant only at the 5 % level between the poor risk groups Undoubtedly the need of hospital treatment increases as a population grows older, but there are two facts that explain the apparent reduction of morbidity since 1960 Firstly, those with the most advanced disease, most in need of hospital facilities are already dead Secondly, these old patients, when chronically ill, have not been admitted to this hospital but to the geriatric service and have then had to be withdrawn from the study

Effect on anginal pain

As the experiment was made double blind we hoped to get an opportunity to study the effect on angina pectoris As usual, this subjective complaint has been very difficult to evaluate We have, however, tried to estimate the severity of anginal pain by letting the other physicians of the clinic note on every visit of the patients their average consumption of nitroglycerine, their ability to walk on stairs etc and their own judgement (better, unchanged, worse) From these notes we have got the following table (table IX) In this table are included patients with anginal pain on effort for more than 2 weeks before the initial hospital admission and with an observation time in the trial of 2 years or more

The figures suggest some beneficial effect In our opinion it is natural to see this as a result of the lower frequency in the dicumarol series of reinfarctions and thromboembolic complications

Hemorrhage

All patients were instructed to report even small bleedings. This tends to make the total number of hemorrhagic complications quite large, but the comparison between dicumarol and placebo groups will not suffer. Table X shows all hemorrhages reported during the study. Of the 42 patients still on dicumarol 24 have experienced 47 bleeding complications during a total of 3,307 observation months, making a frequency of 14 per thousand observation months. For the whole dicumarol series the frequency is 20, i.e. one in slightly more than four years. The corresponding figure for placebo patients is 5 per thousand months.

The types of bleeding that dominate in the dicumarol series are hematuria, superficial bruising, epistaxis and gastrointestinal blood, which may in several cases be due to nose bleeding.

The central nervous bleedings are to be most feared and make anticoagulation very doubtful in every person of 60 or more with a permanent diastolic blood pressure of 110 or more.

The frequency of bleeding seems to increase approximately three times at a PP level below 10 % (the relatively short times on those low values taken into account).

The intensity of the anticoagulant therapy

To judge the intensity of the anticoagulant effect we have used the same criteria as Waaler (16).

Good intensity = 69 % or more of the PP values are 30 % or less.

Fair intensity = 39—68 % of the PP values are 30 % or less.

TABLE X. Bleeding complications

	Dicumarol series PP level (%) <10	10—30	>30	Placebo series
Fatal				
Cerebral hemorrhage	1	3	1	2
Gastrointestinal	1	—	—	2
Rupture of myocardium	—	—	—	1
Rup. of aortic aneurysm	—	—	—	1
Non fatal				
Hematuria slight	10	11	—	1
Hematuria severe	—	1	1	1
Gastrointestinal	5	8	3	5
Hematoma large	5	8	1	1
Hematoma small (bruises)	10	9	3	5
Epistaxis	6	6	2	6
Hemorrhoidal	—	5	—	3
Hemoptysis	—	1	—	—
Meningeal	—	1	—	—
Intra cerebral	—	—	1	—
Retinal	—	—	1	—
Total	38	53	13	28 in
	104 in 76 pat			17 pat

TABLE XI. Intensity of anticoagulant treatment

	Good	Fair	Poor	Total
Males	48	25	3	76
Females	25	17	0	42
Living and withdrawn	46	32	1	79
Dead	27	10	2	39
Good risk	27	13	0	40
Poor risk	46	29	3	78

TABLE XII Frequency of initial poor risk criteria in still living and in dead patients

	No of poor risk pat	Percentage of pat with						
		Previous infarction	Previous thrombotic disease	Heart dilatation	Congestive failure	Rhythm disturb	Hypercholesterolemia	Obesity
Dicumarol series								
Living	21	14	19	52	14	19	24	19
Dead	34	26	12	68	50	44	12	3
Total	55	22	15	62	36	35	16	10
Placebo series								
Living	21	24	5	38	21	10	19	5
Dead	45	13	11	62	31	33	11	2
Total	66	17	9	55	29	26	14	3

Poor intensity = less than 39% of the PP values are 30 % or less

Intentionally high values at any interruption of the therapy are excluded

The number of patients in each intensity group is shown in table XI No differences between sexes, dead or living patients, good or poor risk patients can be seen Within the group of good intensity some patients have shown surprisingly stable blood values and a constant dicumarol dosage through several years The group is too small to allow of any comparison with the group of patients showing large fluctuations

The value of different poor risk criteria

The criteria of Russek et al (12) of poor risk in acute myocardial infarction are

1 Previous infarction
2 Intractable pain
3 Extreme degree or persistence of shock
4 Significant enlargement of the heart
5 Gallop rhythm
6 Congestive failure
7 Auricular fibrillation or flutter, ventricular tachycardia or intraventricular block
8 Diabetic acidosis, marked obesity, previous pulmonary embolism, varicosities of the lower extremities thrombophlebitis or other states predisposing to thrombosis

We applied these criteria on the patients surviving their first hospital stay thus not in the acute phase of their illness Therefore some of the criteria (points 2 3 and 5) have occurred only in a few instances The importance for the long term prognosis of some of the other criteria is seen from table XII The following definitions have been used

Heart enlargement = relative volume > 450 in women and > 500 in men
Hypercholesterolemia = serum value of > 300 mg %
Marked obesity = body weight ≥ (length in cm — 80) kg

From this table it is seen

1 The placebo patients have generally had a little better start than the dicumarol patients
2 Hypercholesterolemia and obesity have had little influence on the prognosis during the next few years
3 Previous myocardial infarction is not necessarily a grave prognostic sign
4 Heart dilatation congestive failure and rhythm disturbances are grave prognostic signs In acute myocardial infarction, Honey and Truelove (7) and Griffith et al (8) have found the same factors to be the most important

The small number of survivors with a previous infarction in the dicumarol series again depends on the large number of sudden deaths during the first year Myocardial infarction predisposes to such a mode of death which can not be prevented by anticoagulants The figures of previous thromboembolic disease (including intermittent claudication) are small, but suggest a prophylactic effect of antioagulants for that group of patients

The decisive criteria in the selection of patients for long term anticoagulant prophylaxis should probable be previous thromboembolism (including, but not particularly stressing the role of myocardial infarction), heart dilatation and rhythm disturbances of permanent type

Diabetes was not considered a poor risk criterion and was not taken into account in the primary subgrouping Therefore, the incidence of diabetes in the two series is somewhat, but not significantly different In the dicumarol series, 8 patients with diabetes were included 4 of them died during the observation period In the placebo series there were 13 diabetics of whom 7 died From the large study of Sievers (15) it appears that diabetes should not alter the long term prognosis of mycardial infarction

Discussion

Nobody will deny that anticoagulants of the indirect type, such as dicumarol, have an excellent preventive effect on deep venous thrombosis, pulmonary embolism and arterial embolism In these cases the primary thrombus is formed in slowly running blood and is rich in fibrin

The preventive effect on arterial thrombosis and myocardial infarction is less evident (5 6 9, 10, 13, 14) An indirect evidence of an antithrombotic effect is however, the common occurrence of arterial occlusions when a long term anticoagulant treatment is suddenly (and sometimes *unnecessarily*) stopped because of bleeding or surgery

The indirect anticoagulants have little effect on platelet adhesiveness (11) On theoretical grounds it seems reasonable that they should have little antithrombotic effect in vessels small enough or narrowed enough to be occluded by a thrombocyte plug poor in fibrin Many intracerebral and myocardial artery branches probably have such a critical diameter from the beginning or need very little atheromatous change to reach

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it In arteries of a larger diameter more fibrin deposition will be necessary to get an occlusion and a better protective effect from anticoagulants might be expected

As a rule, one can expect that any therapeutic or prophylactic effect of a treatment would improve most the prospects of the patients with the most unfavourable prognosis (1, 9) Thus, it is reasonable to assume that the large proportion of poor risk patients in the present material has made it possible for us to show for that group a statistically significant reduction of myocardial infarctions, cerebral infarctions and thromboembolism and some effect on mortality In some other materials the proportion of good/poor risk patients may have been such as to obscure the effect (3, 4, 5, 6, 13) The results of this study seem to show that in the small group of good risk patients there was little or nothing to gain by long-term anticoagulant prophylaxis In patients with a tendency to thromboembolism it is possible, successfully to reduce the number of such complications

As we see it today, an antithrombotic effect is the only result one can hope to achieve by anticoagulant treatment of patients with advanced arterial disease It will thus be logical to select for long term prophylaxis the patients in whom thromboembolic complications are more common than in others Today there are no tests available to select patients who are threatened by thrombosis We therefore would like to give the guiding criteria for such a selection of patients with coronary heart disease the following ranking order

1 Heart enlargement with auricular fibrillation
2 Previous venous or arterial thrombosis or multiple arterial stenoses
3 Ventricular aneurysm or transmural myocardial infarct
4 Congestive failure
5 Heart enlargement with sinus rhythm
6 Permanent immobilization

Arterial embolism is always a reason for life-long anticoagulant therapy (if the cause cannot be definitely eliminated) and is therefore not included in the list

If any 'good risk" patients should later develop one or more of the criteria mentioned above, anticoagulant prophylaxis should be reconsidered

In every patient with heart disease, anticoagulants will be of value as a prophylaxis against venous thrombosis during a period of strict bed rest As soon as the 'thromboembolic prognosis" has been assessed and some physical activity can be resumed, anticoagulants then could be discontinued in patients with a 'good risk" In patients with a disabling angina after an episode of myocardial infarction the probable arterial stenosis and the physical disability together will probably be a reason to continue Therefore, it is sometimes wise to wait for the patient's reaction to the strain of his ordinary occupation before the decision is made

The recent discussion about anticoagulant prophylaxis in atherosclerotic heart disease has caused much uncertainty among Swedish physicians Many of them, who have found the management of anticoagulant treatment troublesome, are now abandoning it altogether Certainly, that is an unnecessary step

backwards It will be more realistic however, to look on the anticoagulants, now available as valuable aids in advanced cardio-vascular disease rather than to strive to hold for them a position in the early prevention of such disease

Summary

In order to study the antithrombotic effect of dicumarol prophylaxis in atherosclerotic heart disease, two comparable groups of patients, mostly survivors after myocardial infarctions, have been followed for $5^1/_2$—8 years The group on dicumarol initially held 118 patients and the placebo group 113 patients both with an average age of 63 5 years In the dicumarol series 78, and in the placebo series 80 patients filled the poor risk criteria of Russek et al During a total of 5205 (dicumarol) and 5510 (placebo) observation months deaths and withdrawals reduced the number of dicumarol patients to 42 and the placebo patients to 45 survivors The overall mortality and the 5 year survival rate were not significantly changed by the prophylaxis but the mortality through 2nd—5th years was in all probability significantly reduced in poor risk patients on dicumarol ($P < 0.05$) The incidence of myocardial infarctions cerebral infarctions and other thromboembolic complications was significantly lowered in the poor risk patients on dicumarol In good risk patients the two series showed equally low mortality and incidence of thromboembolism It is concluded that good risk patients will probably get very little benefit from long term anticoagulant prophylaxis, which ought to be reserved for patients with a permanently increased risk of thromboembolism The criteria for such a selection are discussed

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In order to study the antithrombotic effect of dicumarol prophylaxis in atherosclerotic heart disease, two comparable groups of patients, mostly survivors after myocardial infarctions have been followed for 5 1/2—8 years The group on dicumarol initially held 118 patients and the placebo group 113 patients both with an average age of 63 5 years In the dicumarol series 78, and in the placebo series 80 patients filled the poor risk criteria of Russek et al During a total of 5205 (dicumarol) and 5510 (placebo) observation months deaths and withdrawals reduced the number of dicumarol patients to 42 and the placebo patients to 45 survivors The overall mortality and the 5 year survival rate were not significantly changed by the prophylaxis but the mortality through 2nd—5th years was in all probability significantly reduced in poor risk patients on dicumarol ($P < 0.05$) The incidence of myocardial infarctions cerebral infarctions and other thromboembolic complications was significantly lowered in the poor risk patients on dicumarol In good risk patients the two series showed equally low mortality and incidence of thromboembolism It is concluded that good risk patients will probably get very little benefit from long term anticoagulant prophylaxis, which ought to be reserved for patients with a permanently increased risk of thromboembolism The criteria for such a selection are discussed

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it In arteries of a larger diameter more fibrin deposition will be necessary to get an occlusion and a better protective effect from anticoagulants might be expected

As a rule, one can expect that any therapeutic or prophylactic effect of a treatment would improve most the prospects of the patients with the most unfavourable prognosis (1, 9) Thus, it is reasonable to assume that the large proportion of poor risk patients in the present material has made it possible for us to show for that group a statistically significant reduction of myocardial infarctions, cerebral infarctions and thromboembolism and some effect on mortality In some other materials the proportion of good/poor risk patients may have been such as to obscure the effect (3, 4, 5, 6, 13) The results of this study seem to show that in the small group of good risk patients there was little or nothing to gain by long term anticoagulant prophylaxis In patients with a tendency to thromboembolism it is possible, successfully to reduce the number of such complications

As we see it today, an antithrombotic effect is the only result one can hope to achieve by anticoagulant treatment of patients with advanced arterial disease It will thus be logical to select for long term prophylaxis the patients in whom thromboembolic complications are more common than in others Today there are no tests available to select patients who are threatened by thrombosis We therefore would like to give the guiding criteria for such a selection of patients with coronary heart disease the following ranking order

1 Heart enlargement with auricular fibrillation
2 Previous venous or arterial thrombosis or multiple arterial stenoses
3 Ventricular aneurysm or transmural myocardial infarct
4 Congestive failure
5 Heart enlargement with sinus rhythm
6 Permanent immobilization

Arterial embolism is always a reason for life-long anticoagulant therapy (if the cause cannot be definitely eliminated) and is therefore not included in the list

If any "good risk" patients should later develop one or more of the criteria mentioned above, anticoagulant prophylaxis should be reconsidered

In every patient with heart disease, anticoagulants will be of value as a prophylaxis against venous thrombosis during a period of strict bed rest As soon as the "thromboembolic prognosis" has been assessed and some physical activity can be resumed, anticoagulants then could be discontinued in patients with a "good risk" In patients with a disabling angina after an episode of myocardial infarction the probable arterial stenosis and the physical disability together will probably be a reason to continue Therefore, it is sometimes wise to wait for the patient's reaction to the strain of his ordinary occupation before the decision is made

The recent discussion about anticoagulant prophylaxis in atherosclerotic heart disease has caused much uncertainty among Swedish physicians Many of them, who have found the management of anticoagulant treatment troublesome, are now abandoning it altogether Certainly, that is an unnecessary step

backwards It will be more realistic, however, to look on the anticoagulants, now available as valuable aids in advanced cardio-vascular disea e rather than to strive to hold for them a position in the early prevention of such disease

Summary

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From the University Endocrinological Laboratory, Rikshospitalet, and Medical Department IX Ullevaal Hospital Oslo Norway

Plasma 17-Hydroxycorticosteroid Responsiveness to ACTH in Patients with Bronchogenic Carcinoma Without Cushing's Syndrome

By

TRULS BRINCK JOHNSEN and JAN H SOLEM

The association between malignancy and hyperadreno-corticism is well known in neoplasms of the adrenal cortex and of the pituitary gland Cushing s syndrome however occasionally develops in patients with tumors of non endocrine origin Since Brown (3) in 1928 published a case report fully characteristic of Cushing s syndrome with oat cell carcinoma of the lung proved at autopsy, evidence has accumulated suggesting that this relation is more than coincidental A number of such cases have been reported in association with many different types of tumors The most common concurrent malignancy has been bronchogenic carcinoma which in almost every case of simultaneous Cushing s syndrome has been of the oat cell type The next most common tumor is thymoma and the third is carcinoma of the pancreas (15)

The idea that the tumor might in some manner stimulate the pituitary to secrete ACTH was suggested by the finding of elevated plasma ACTH levels in several patients (2) Recently Cushing s syndrome in cases of carcinoma of the lung has been attributed to a corticotropin like material extractable directly from the tumor (9 12) Adrenocortical hyperplasia has been reported as a post mortem finding in patients with lung cancer with or without overt Cushing s syndrome (8) An adrenal weight maintaining factor in the blood of patients with Cushing s syndrome from pulmonary neoplasms has been reported (4) Possibly there are two types of corticotropin a steroid releasing type causing the Cushing s syndrome and a second weight maintaining corticotropin causing the adrenal cortical hypertrophy A recent finding of an adrenal weight-maintaining factor in two cases of carcinoma of the lung without Cushing s syndrome but with adrenal hypertrophy was therefore not unexpected (13)

Submitted for publication March 18 1964

In most reports on patients with Cushing's syndrome in association with extra-adrenal cancer, attention has been drawn to distinctive changes in plasma electrolyte concentrations,—hypokalemia and alkalosis being conspicuous abnormalities Although basal levels of urinary steroids have been recorded in a number of patients, only occasional reference has been made to the response to ACTH administration in such patients (1, 6, 7, 17)

The aim of the present study was a quantitative appraisal of adrenal cortical functional capacity in a number of patients in whom radiographic examination had revealed an intrathoracic lesion This appraisal was carried out by means of a standardized test for adrenal cortical stimulation by intramuscular administration of a repository ACTH preparation We were interested to learn whether such a test warranted use of in patients with pulmonary lesions to establish a diagnosis of bronchogenic carcinoma The patients were divided into four groups, the main group being 45 patients with bronchogenic carcinoma

Material

Group 0

This control group included 62 representatives of the varied clientele of a medical department over 3 years (16) None of them was suffering from lesions affecting the endocrine glands or from malignant diseases or was running a fever at the time of the test

Group 1

This group included 45 patients with bronchogenic carcinoma who were hospitalized over a 3 year period (1961—1963) There was histologic confirmation of bronchogenic carcinoma in all cases Of these 45 patients the proportion of individual cell types was as follows squamous 23, adenocarcinoma 8, undifferentiated 7, oat 5 mixed squamous and undifferentiated 1, large cell anaplastic 1

There was no clinical evidence of Cushing's syndrome or mineralocorticoid excess in any of these patients The serum potassium and carbon dioxide levels were normal in all cases at the time of study Abnormalities in carbohydrate metabolism, particularly an increased fasting glucose concentration, were observed in a few cases as has been observed in various types of cancer (11) Evidence of tumor growth in these patients with a few exceptions was restricted to the lungs or to the lungs and regional lymph nodes demonstrated either radiographically or surgically Bedridden patients with advanced cancer were excluded and no patient was included in this group if death occurred within 4 weeks from the time of study All had symptoms and varying clinical evidence of their disease Most of the patients had fever, 100 to 102° F at the time of study Weight loss was marked in about one third of the group At the time of study none presented obvious central nervous system dysfunction pointing to brain involvement of the malignant disease

Group 2

This group included 13 patients who had malignant intrathoracic tumors other than bronchogenic carcinoma Two patients had malignant thymoma Eleven patients had solitary pulmonary metastases from neoplasms in the uro genital tract or in the gastro-intestinal tract (including 3 patients with carcinoma of the pancreas) They were hospitalized under the diagnosis of lung cancer after previous radiographic examination All patients had varying clinical evidence of their malignant disease There were no clinical features of Cushing's syndrome in these 13 patients No patients was bedridden but some of them were in serious distress at the time of study Patients who died within four weeks from the time of study were not included in the group

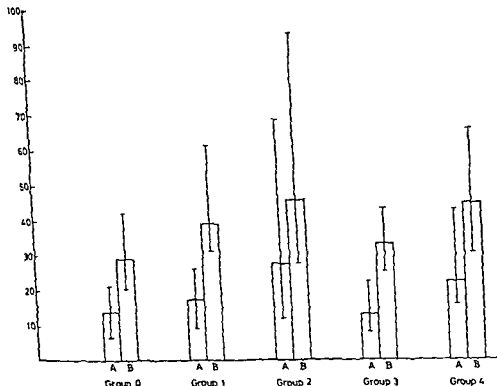


Fig 1 Each bar represents the mean levels of plasma 17 hydroxycorticosteroids (17 OHCS) with range of observations indicated A 8 a m B 12 00 4 hours after ACTH administration Group 0 6? controls. Group 1 45 patients with bronchogenic carcinoma Group 2 13 patients with malignant neoplasms other than bronchogenic Group 3 11 patients with benign coin lesions of the lungs Group 4 12 patients with uncomplicated pneumonia

Group 3

This group included 11 patients with solitary pulmonary coin lesions which after exploratory thoracotomy with biopsy proved to be tuberculoma 6 non-specific chronic inflammation 3 organized pneumonia 1 hamartoma 1 All cases but one were discovered on routine chest roentgenograms and were asymptomatic or nearly so

Group 4

This group included 12 patients who were admitted to the hospital with the diagnosis of pneumonia and the hospital course and the follow up supported this diagnosis At the time of study they all had fairly characteristic symptoms and signs of the disease and without exception were running a fever of 102° F or more

Methods

Free plasma 17 hydroxycorticosteroids were determined by a modification of the method described by Eik Nes (5) The plasma samples were extracted with methylene chloride with use of conical glass-stoppered tubes in a mechanical shaker After the extracts had been washed with 0 1 N NaOH they were evaporated to dryness under nitrogen and a

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ma of the lung may be due in most cases to an effect of chronic and severe illness not specific for bronchogenic carcinoma (13) The diagnostic value of the test in an individual case where a pulmonary lesion has been discovered on a chest roentgenogram seems to be almost nil Significant hyperresponsiveness to the ACTH test was not found in our patients with benign coin lesions of the lungs On the other hand, twenty three of the 45 patients with bronchogenic carcinoma had a normal response to the test Among the patients with neoplasms other than bronchogenic, hyperresponsiveness to the test was found in eleven out of 13 patients, and in fact some of the highest responses were found in this group In group 1 we did not find especially marked hyperresponsiveness in the five patients with oat cell carcinoma in comparison with the whole group of 45 patients with carcinoma of the lung Pneumonia, which so often is a complication to bronchogenic carcinoma was the underlying cause of the hyperresponsiveness to the ACTH test which was found in eleven out of 12 cases in group 4 At the time of study all these patients were acutely ill One to three months after discharge from the hospital all eleven patients were re tested and the result of the ACTH test was then found to be normal

Summary

In a group of fourty five patients with bronchogenic carcinoma without overt Cushing's syndrome, hyperresponsiveness of plasma 17 hydroxycorticosteroid levels to a standardized ACTH test could be demonstrated The response, however, did not differ significantly from that to the same test in a group of patients with other tumors of non endocrine origin The same hyperresponsiveness was also found in a group of patients with pneumonia The authors therefore feel it unjustified to carry out a 'screening' ACTH test in patients where a radiographical examination has revealed an intrathoracic lesion in order to make an indirect approach to the diagnosis of bronchogenic carcinoma

Acknowledgement

This work was supported by a grant from Grosserer N A Stangs legat til kreftsykdommers bekjempelse Grateful acknowledgement is made to Mrs Kari Brinck Johnsen for her valuable technical assistance

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The adrenal cortical response to ACTH was evaluated by taking a 10 ml heparinized blood sample at 8 a m at which time 40 units of a repository ACTH preparation (Jaton prolongatum) were given intramuscularly Another blood-sample was obtained 4 hours later Free 17 hydroxycorticosteroids (17-OHCS) were estimated in the two samples, using 5 ml of plasma per analysis (16)

Results

The ACTH test was carried out in 143 individuals Fig 1 presents the mean levels of 17-OHCS in plasma at the beginning (A) and at the end (B) of the test The range of the observations is indicated on each bar In the light of our experience we take the maximum values as an index of adrenal responsiveness to ACTH — and not the increments relative to starting levels To express the result of the test by calculating the maximum value as per cent of the basal value is nonsensical (16) Group 0 62 controls, group 1 45 patients with bronchogenic carcinoma, group 2 13 patients with malignant neoplasms other than bronchogenic, group 3 11 patients with benign coin lesions of the lungs group 4 12 patients with uncomplicated pneumonia

Discussion

The results indicate an abnormality in adrenal steroid metabolism in patients with bronchogenic carcinoma This abnormality is characterized by hyperresponsiveness of plasma 17-OHCS levels to a standardized ACTH test The response, however, does not differ significantly from that in patients with neoplasms other than bronchogenic The same hyperresponsiveness was also found in patients with pneumonia where bronchogenic carcinoma could be excluded as an underlying contributory factor

We should like to emphasize that an increase in the plasma 17 OHCS response to ACTH in a sick patient does not necessarily indicate an increased adrenocortical secretion of cortisol The result of an ACTH test will be influenced by the capacity of the plasma proteins to bind cortisol and the ability of the organism to metabolize cortisol It was, however, not the aim of this study to solve this side of the problem We were primarily interested in getting answers to the following questions Is it worth while to carry out a "screening" ACTH test in patients with pulmonary lesions in the absence of Cushing s syndrome? Does a hyperresponsiveness of plasma 17-OHCS levels to such a test make the diagnosis of a bronchogenic carcinoma highly possible in these patients? Our conclusions, based on the results of our study, are negative We do not deny that certain tumors (particularly undifferentiated bronchogenic carcinomas) autonomously elaborate an ACTH-like substance that stimulates the adrenal glands to secrete large quantities of corticoids (12) The evidence of our study, however is consistent with the hypothesis that an increased plasma 17-OHCS responsiveness to ACTH seen in patients with carcino-

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From the Renal Unit, Department of Endocrinology and Metabolic Diseases, University Hospital Leiden, the Netherlands

The Incidence of Phaeochromocytoma in the Netherlands

By

J DE GRAEFF and B J V HORAK

Phaeochromocytoma a tumour of the chromaffin cells of the sympathetic nervous system is usually considered to be a rare condition In 1886 Fraenkel (12) described the autopsy of a young woman with bilateral tumours of the adrenal medulla In a critical analysis he ascribed the pulsus durus and the changes in the eye grounds, which had been present during life, to a substance which was produced by these tumours This is considered to be the first complete description of a secreting phaeochromocytoma

Graham (16) was able to collect some 207 cases from the literature up to 1949 According to Symington (39) only 160 cases had been described up to 1947 but 120 more were reported in the ensuing few years Most recent authors feel that phaeochromocytoma is being diagnosed in vivo with increasing frequency partly because the characteristic clinical syndrome caused by the secretion of norepinephrine and epinephrine has been duly recognised and partly because valid and relatively precise methods for the diagnosis have been developed Nothing is known about its true incidence Smithwick (cited by Aranow (37)) found 8 cases in a series of 1,700 hypertensive patients who had been referred to him for sympathectomy, i e 4 7 per mille, but the select nature of this group does not permit an appreciation of the actual incidence of phaeochromocytoma

In an effort to shed some light on this problem we sent a questionnaire to all the Institutes of Pathology in the Netherlands They were asked to report all the phaeochromocytomas found during the period of January 1st 1949 until January 1st 1959 in surgical specimens as well as in autopsy material We then proceeded to get information about the clinical status of the patients thus reported by contacting the physicians under whose care they were at the time of their operation or death The results of these enquiries will be presented in this communication The main data are summarised in table I

Some of these cases have already been published (ten Berge (2) No 22 Bruyns

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TABLE I Main clinical data

No	Sex	Age (yrs)	Duration of symptoms (yrs)	Site of tumour[1]	Diagnosed	Result of op[2]	Remarks
1	♂	28	1	LK	Yes	N	—
2	♂	17	5	Th	Yes	N	—
3	♀	56	6	Th	Yes	N	—
4	♀	40	8	RA	Yes	N	Neurofibromatosis, died one year later of coecum carcinoma
5	♂	33	1	RA	Yes	N	—
6	♂	8	1	RA	Yes	N	—
7	♂	31	10	Mult	Yes	N	High familial incidence of phaeochromocytoma (cf no 31)
8	♂	28	2	LA	Yes	N	—
9	♀	42	?	LA	Yes	H	—
10	♀	39	5	RA	Yes	N	—
11	♀	57	4	RA	Yes	N	—
12	♂	50	6	LA	Yes	H	—
13	♀	20	3	RA	Yes	H	—
14	♀	39	3	LA	Yes	N	—
15	♀	41	?	RA	Yes	H	—
16	♂	65	1/12	LA	Yes	N	—
17	♂	14	2	RA	Yes	N	—
18	♀	50	13	LA	Yes	H	—
19	♀	20	?	LA	Yes	?	—
20	♀	37	?	Mult	Yes	†	Died after removal RA multiple phaeochromocytomas thyroid carcinoma
21	♂	55	8	RA	Yes	†	Died after removal phaeochromocytoma megacolon
22	♂	15	1/4	RA	Yes	†	Diagnosis made after left sympathectomy, died during 2nd op
23	♀	54	1/2	LA	Yes	†	Died postoperatively of cerebrovascular accident multiple cysts in RK
24	♀	15	4	LA	Yes	†	Died during op sister operated in 1943 for phaeochromocytoma
25	♀	23	3	Mal	Yes	Metast	Phaeochromocytoma RA removed 1953 RK 1956 pulmonary metastases after 9 years
26	♂	57	1 1/2	Mal	Yes	Metast.	Died of hepatic metastases after 6 years
27	♂	51	3/4	RA	Yes	—	Died suddenly before op pulmonary embolism
28	♂	23	1/12	LA	Yes	N	Chance finding during nephrectomy for hydronephrosis No previous data
29	♀	60	18	LA	No	—	Clinical history suspect histamine test neg catecholamine-excretion normal died of cerebrovascular accident

TABLE I (cont)

No	Sex	Age (yrs)	Duration of symptoms (yrs)	Site of tumour[1]	Diagnosed	Result of op[2]	Remarks
30	♀	42	10	RA	No	—	Admitted in shock clinical history suspect
31	♂	62	?	Mult	No	—	High familial incidence of phaeochromocytoma thyroid carcinoma clinical history suspect died of shock
32	♀	62	1/2	LA	No	—	Burst aneurysm of a cerebri media chronic hypertension with paroxysmal dyspnoea
33	♀	60	1	Th	No	—	Died during bronchoscopy clinical history suspect
34	♀	55	1/2	LA	No	—	Clinical history suspect shock shortly after admission
35	♂	46	6	Mult	No	—	Clinical history suspect dehydration septicaemia? tabes dorsalis
36	[illegible]	26	?	RA	No	—	Subarachnoid haemorrhage admitted in shock hypertension during pregnancy
37	[illegible]	51	16	LA	No	—	Cerebrovascular accident clinical history suspect
38	[illegible]	28	1	RA	No	—	Neurofibromatosis died after gastric resection clinical history suspect
39		67	[illegible]	RA	No	—	No previous history died of irreversible shock
40	♂	59	?	RK	No	—	Chronic hypertension burst aneurysm of abdominal aorta no symptoms of phaeochromocytoma previously
41	[illegible]	67	4	RA	No	—	Chronic hypertension diabetes mellitus no symptoms of phaeochromocytoma myocardial infarction
42	[illegible]	47	[illegible]	LA	No	—	Neurofibromatosis glioma cerebri no previous history shock
43	[illegible]	55	[illegible]	RA	No		No previous history pneumonia sudden death
44		74	[illegible]	LA	No	—	Died of peritonitis no previous history

[1] RA and LA right and left adrenal RK and LK hilus of right and left kidney Th thorax Mult bilateral or multiple Mal malignant

N normotensive H hypertensive ? unknown † died during or shortly after operation Metast metastases — not operated

TABLE II Incidence of phaeochromocytoma in the Netherlands (1949—1959)

Year	Population	Deaths[1]	Phaeochromocytoma		
			Diagnosed	Undiagnosed	Total
1949	9,955,594	81,077	4	—	4
1950	10 113 527	75,580	2	—	2
1951	10 264,311	77,194	1	—	1
1952	10 381,987	75,986	5	1	6
1953	10 493 184	80 551	2	2	4
1954	10 615 380	79,295	1	1	2
1955	10,750 842	81 364	1	—	1
1956	10 889,351	84 521	4	3	7
1957	11,026 383	82,677	3	3	6
1958	11,186,875	84 175	5	6	11
	Total	802 420	28	16	44

[1] An autopsy was performed in 10 %

Slot (3) No 8, De Graeff Muller and Moolenaar (15) No 1, 2 3, 20 25, 30, 40, Hulst (20) No 21, van Schie (32) No 4, 5, 6, 21, Schroder (33) No 38, Smits (38) No 7, 31, Viersma, de Vaal Kemp (40) No 12)

It is evident that this type of study is subject to some criticism During the period of study several Institutes of Pathology did not have a regular index system Moreover during a routine autopsy a phaeochromocytoma may have easily escaped recognition, especially if it was in an unusual location Thus the figures given for the undiagnosed cases found at autopsy are probably too low, while those given for the operated cases may be more realistic

Furthermore, a retrospective review of the signs and symptoms of a disease is apt to be incomplete as many pertinent questions and investigations may have been omitted

In 23 out of the 28 Institutes of Pathology existent in the Netherlands in the spring of 1959 the questionnaire was filled out and returned The report covers a total of approximately 80,000 autopsies over a period of ten years

Results

Incidence of phaeochromocytoma

During this period 44 cases of phaeochromocytoma were recorded The diagnosis had been made during life in 28 cases In 16 the phaeochromocytoma was a chance finding at autopsy (table II) There does not seem to have been an improvement in clinical diagnosis during this period, although the numbers are too small to warrant a definite statement It thus appears that the major advance in diagnostic procedures had already occurred before 1949 In table II are also mentioned the total annual population figures and number of deaths in this country for the years 1949 through 1959 An autopsy was performed in approximately 10 % of cases According to the Centraal Bureau voor de Statistiek" it can be estimated that hypertension was the main cause of death in some 24,000 Although the restrictions mentioned above preclude

of any definite conclusions a few speculations can be made about incidence An undiagnosed phaeochromocytoma was found in at least 0 2 per mille of the autopsies These cases will be discussed in more detail later on Minno et al (27) reported 12 undiagnosed cases in a series of nearly 16 000 autopsies (0 75 per mille) If the autopsy material was a representative sample of all deaths and if the undiagnosed cases of phaeochromocytoma died of hypertension, 6 per mille of the hypertensive patients might have had a phaeochromocytoma This figure albeit a very rough approximation is of the same order of magnitude as the one mentioned by Smithwick

Sex and age incidence

The distribution of phaeochromocytoma among both sexes was about equal (20 men and 24 women) as is usually stated In table III the distribution among the different age groups is given It is clear that phaeochromocytoma is extremely rare in the very young and very old Cone (7) could find only 11 patients less than 10 years old in the literature up to 1957 Otherwise the patients in our series were fairly equally distributed among the different age groups

Familial incidence

Two cases (Nos 7 and 31) belonged to one family which has been extensively studied and described by Smits (38) They both had bilateral tumours In this family a phaeochromocytoma could be demonstrated in four members In 10 other diseased members such a diagnosis seemed to be likely According to this author the mode of inheritance of

TABLE III Age distribution

Age (years)	Phaeochromocytoma
0–9	1
10–19	4
20–29	8
30–39	5
40–49	6
50–59	12
60–69	7
70–79	1

TABLE IV Site of tumour

	This series	Graham (16)
Right adrenal	17	92
Left adrenal	16	70
Multiple growth	4	19
Extra adrenal	5	23
Malignant	2	?
Total	44	204

phaeochromocytoma is a monomeric dominant and autosomal one with variable expression in the phenotype

One case (No 24) had a sister who died of phaeochromocytoma in 1943 Because of war circumstances at that moment no further details could be obtained The familial occurrence of phaeochromocytoma has already been recorded by several other authors (8, 11 17, 21)

Site of tumour

In table IV the site of the tumour is given The distribution agrees quite well with the one given by Graham (16) in his review article Among the 44 cases, multiple phaeochromocytoma unilateral or bilateral were encountered four times and an extra adrenal location five times

This is in agreement with the ten per cent figure which is usually given for their incidence One should beware of statistics in this respect however as one of the four multiple growths and four of the five extra adrenal locations all came from one series of seven cases of phaeochromocytoma (15) In this centre a 'normal" location in one adrenal was encountered only once during this period of ten years An intrathoracic tumour was seen in three patients (No 2, 3, 33) Of interest is the location of a phaeochromocytoma in the fork of the renal artery in two patients (Nos 1, 40)

During this period no location in the urinary bladder was encountered although this has been described (1, 10, 18, 26)

Malignancy

It is difficult to define a malignant phaeochromocytoma because histological criteria such as pleomorphism, presence of neoplastic cells in the veins of the tumour and even invasive growth do not necessarily mean that the tumour will behave as a malignancy Symington et al (39) accepted only 7 cases as definitely malignant They pointed out that even the presence of metastases need not be conclusive evidence of malignancy as the latter may be due to an associated neoplasm Only the presence of phaeochromocytoma at a site where chromaffin tissue does not exist normally, can be considered proof of true secondary deposition and thus of malignancy In the present series a diagnosis of malignant phaeochromocytoma has been made twice (Nos 25, 26) although, strictly speaking, the conditions defined by Symington et al have not been fulfilled

One of the patients (No 25) a woman aged 23 on her first admission had a phaeochromocytoma of the right adrenal removed in 1953 All symptoms subsided, a histamine test was negative and the excretion of catecholamines in the urine was normal on several occasions In 1956 hypertension recurred Another phaeochromocytoma, located in the fork of the right renal artery, was removed Again a complete clinical and biochemical remission occurred She was seen at regular intervals until 1959 and always found to be normotensive In 1962 she was readmitted because of haemoptysis and symptoms suggestive of another phaeochromocytoma The B P was high (170/115 mm Hg) with frequent paroxysms up to 300/180 mm Hg The excretion of 3 methoxy—4 hydroxy mandelic acid was increased (30 mg/day) Radiological examination of the thorax, with tomography, revealed the presence of several pulmonary metastases A tentative treatment with α methyldopa led to a pronounced deterioration of her condition with periods of orthostatic hypotension followed by severe overshooting of blood pressure

The administration of dibenzyline resulted in a complete remission of all symptoms and she has remained well until now

In the second patient (No 26), a man aged 57 on his first admission, a laparotomy was performed in 1949 because of an abdominal mass A tumour with the histological appearance of a phaeochromocytoma weighing 3 5 kg, located in the left adrenal was removed In 1953 a second tumour with the same histological appearance and located in the omentum was removed In 1955 the patient died of pulmonary metastases histologically similar to the original adrenal neoplasm Unfortunately no data were available about the blood pressure or the secretion of catecholamines

Concurrent abnormalities

Neurofibromatosis The combination of phaeochromocytoma with neurofibromatosis has been noted by several authors (4 13, 22, 33, 35) Glushien et al (13) extended this observation to the entire neurocutaneous syndrome (neurofibromatosis, von Hippel Lindau disease, tuberous sclerosis and Sturge Weber syndrome) and estimated that at least ten per cent of patients with phaeochromocytoma would be found to have some form of this complex of diseases

In the present series neurofibromatosis was encountered three times

In the first patient (No 4), a woman aged 40 a phaeochromocytoma of the right adrenal was removed successfully (32) She died about a year later from a carcinoma of the caecum

In the second patient (No 42) a man aged 47 a phaeochromocytoma of the left adrenal was found at autopsy as well as a cerebral glioma The third patient (No 38) a man aged 28 was operated on for pyloric stenosis (33) He died at the end of the operation A phaeochromocytoma of the right adrenal was found at autopsy Two of these patients thus had neurofibromatosis associated with a phaeochromocytoma of the right adrenal This is not in agreement with the preponderance of location in the left adrenal as mentioned by Glushien et al (13)

Thyroid carcinoma

In two patients an anaplastic thyroid carcinoma associated with bilateral phaeochromocytoma (Nos 20, 31) was found

The first patient (No 20) a woman aged 37 died shortly after the removal of a phaeochromocytoma of the right adrenal (15) At the autopsy a phaeochromocytoma of the left adrenal several paraaortic gangliomas and an anaplastic thyroid carcinoma with pulmonary metastases were found The other patient (No 31), belonged to a family with a large incidence of phaeochromocytoma already mentioned (38) He was admitted to the hospital in a state of shock and died within a few hours At autopsy a phaeochromocytoma of both adrenals and a thyroid carcinoma with hepatic metastases were discovered In both patients the physician in charge was impressed by the coarse features which reminded him of acromegaly

The incidence of thyroid carcinoma in patients with phaeochromocytoma was considered to be increased far beyond expectation based on chance concurrence by Sipple (36), who was able to collect seven cases from the literature (including patient No 20 of the present series)

Four of these had bilateral phaeochromocytoma Furthermore Rothermick (31) described another patient with bilateral phaeochromocytoma and an adenocarcinoma of the thyroid gland

Other disorders

Constipation can be one of the symptoms of phaeochromocytoma In case 21 a megacolon associated with a phaeochromocytoma was recorded The patient died during an emergency operation because of intestinal obstruction (20) This association has also been described by Shockett and Teloh (35)

Signs and symptoms

Although paroxysmal hypertension with normal blood pressure between the attacks was originally considered to be the only typical manifestation of phaeochromocytoma, in later years it has become clear that sustained hypertension with superimposed paroxysmal hypertension is much more frequent In this series paroxysmal hypertension alone was en

TABLE V Signs and symptoms The numbers within brackets indicate the number of patients in whom the data were recorded

Only paroxysmal hypertension	3
Only sustained hypertension	5
Sustained hypertension with paroxysms	27
No hypertension recorded	6
Blood pressure unknown	3
Abnormal ECG	21 (33)
Changes in eyegrounds	[1]17 (24)
Decreased renal function	2 (30)
Proteinuria	25 (34)
Tachycardia	28 (34)
Headaches	26 (32)
Perspiration	21 (30)
Pallor	18 (26)
Weight loss	13 (31)
Hyperglycaemia	14 (27)
Hypermetabolism	9 (18)

[1] Grade I—II 8, grade III—IV 9

TABLE VI Diagnostic and localising procedures The numbers within brackets indicate the number of patients in whom the data were recorded

Histamine test positive	9 (12)
Phentolamine test positive	11 (12)
Piperoxane test positive	10 (14)
TEAB test positive	1 (2)
Nitroglycerine test positive	3 (3)
Catecholamines elevated	12 (13)
Intravenous pyelography	9 (21)
Presacral oxygen insufflation	10 (13)

countered only three times (table V) Sustained hypertension, simulating essential hypertension, was nearly as rare (five times) Sustained hypertension with occasional paroxysmal crises was recorded in 27 patients In nine patients insufficient data on blood pressures were available

Electrocardiographic changes suggestive of left ventricular strain and secondary changes in the eye grounds (table V) were quite common Renal function was normal in the great majority of the cases although slight proteinuria was often found In only two cases was an increase in blood urea noted This could be attributed to pyelonephritis in both instances Tachycardia, profuse perspiration and a profound pallor have been quite common findings Weight loss was found in only about half of the cases although marked obesity was extremely rare Hyperglycaemia and hypermetabolism were recorded in about half of the cases in which they were looked for

The combination of weight loss, hypermetabolism, tachycardia and tremors led to an erroneous diagnosis of hyperthyroidism in patient No 8 (3) She was treated as such for more than a year before the diagnosis of phaeochromocytoma was made

Symptoms, which in retrospect could be ascribed to the presence of a phaeochromocytoma, had been present for more than five years in ten out of seventeen cases before the correct diagnosis was made

Diagnostic and localising procedures

During the period of study a whole battery of diagnostic tests had become available (table VI)

The histamine test (30) was positive in nine out of twelve patients in which it was used The phentolamine (Regitine) test (9) has proved to be quite reliable as it was positive in 10 out of 11 patients It should be realised however that this test gives a false positive result in 10—20 % of hypertensive patients Four out of 14 piperoxane test (14) gave false negative results The tetraethylammonium bromide test (TEAB) (23) and

nitroglycerine test (40) were only used incidentally The excretion of catecholamines was estimated by biological or fluorimetric assay in 13 patients It was found to be normal on only one occasion In this patient the histamine and TEAB tests were both negative She was a 60-year-old woman (No 29) with sustained hypertension hyperglycaemia and complaints of paroxysmal abdominal pains Eleven years later she died of a cerebrovascular accident At autopsy a pea sized phaeochromocytoma of the left adrenal was discovered A normal value for catecholamines in the presence of a phaeochromocytoma has been mentioned previously in the literature (25) This however was in connection with a patient with only paroxysmal hypertension in whom such a normal value could be visualised

The other false negative histamine tests were found in the patients Nos 10 11 22 In patient No 10 a phentolamine test and in patient No 22 a piperoxane test was positive In case No 11 the phentolamine test was also negative although a phaeochromocytoma weighing 12 g and localised in the right adrenal was later removed There were no data available on the excretion of catecholamines False negative piperoxane tests were encountered in the patients Nos 2 4 15 and 23 The first two had a positive phentolamine test and the latter two a positive histamine test.

Intravenous pyelography revealed the location of an adrenal tumour in only 9 of 19 patients X rays taken after the presacral insufflation of oxygen were of more help in this respect as they showed the site of the tumour in 10 out of 13 patients

There were no harmful complications from this procedure in this series Aortography however which was performed only once provoked a nearly fatal hypertensive crisis which could only be arrested by the intravenous injection of phentolamine

Operative results

In 19 patients (Nos 1—19) the removal of one or more phaeochromocytomas was successfully undertaken The blood pressure reverted to normal without any recurrence of paroxysms in 13 patients *Sustained hypertension persisted in* 5 patients In one patient (No 19) no post-operative blood pressure readings were available Five patients (Nos 20—24) died of acute pulmonary oedema or irreversible shock during or immediately after the surgical intervention In two patients (Nos 25 and 26), who have already been mentioned the phaeochromocytoma later appeared to have been malignant

One patient (No 27) died quite suddenly from pulmonary embolism before the removal of a diagnosed phaeochromocytoma of the right adrenal could be performed In one patient (No 28) a phaeochromocytoma of the left adrenal was an unsuspected finding during nephrectomy because of hydronephrosis The operation was uneventful There had been no symptoms indicative of a secreting phaeochromocytoma before the operation

Undiagnosed cases

In 16 cases (Nos 29—44) an undiagnosed phaeochromocytoma was found at autopsy In one patient (No 29) who has already been mentioned the diagnosis of phaeochromocytoma was considered but rejected because of a negative histamine and TEAB test and a single normal value for the excretion of catecholamines

In retrospect a history of attacks of headaches, profuse perspiration dizziness, pallor abdominal pains and/or an occasional high blood pressure reading could be elicited in 9 patients (Nos 30—38) Most of these patients died im

mediately or shortly after the last admission to a hospital

In two patients chronic hypertension without any other symptoms of phaeochromocytoma was known to exist (Nos 40—41) In one other patient the presence of cutaneous neurofibromatosis could have suggested a diagnosis of phaeochromocytoma (No 42) In three patients no previous history could be obtained (Nos 39, 43, 44)

Summary

During the period 1949—1959 in the Netherlands a phaeochromocytoma was recorded in 44 patients The diagnosis had been made during life in 28 patients, but the tumour was a chance finding at autopsy in 16 patients The last figure represents 0 2 per mille of the autopsies A phaeochromocytoma could be the cause of hypertension in roughly 6 per mille of hypotensive patients A retrospective review of the signs and symptoms of phaeochromocytoma is given

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Electron Microscopic Study of Liver Mitochondria from Human Alcoholics

By

K -H Kiessling, L Lindgren, B Strandberg and U Tobé

A daily consumption of ethanol for at least six months entails biochemical and histological alterations in liver mitochondria of rats Decreased oxidation rate of certain mitochondrial substrates, decrease in the level of intra and extra mitochondrial thiamine diphosphate and increased activity of certain hydrolyzing enzymes have been observed (3—6) Electronmicroscopic studies reveal a high percentage of markedly malformed mitochondria (7)

In the present paper results are given from an electron microscopic investigation of liver mitochondria from human alcoholics

Methods

The liver biopsies were taken after local anaesthesia with 1 % xylocaine and with a Wim Silvermann needle (outer diameter 2 1 mm) the samples obtained having a diameter of 1 1/2 mm and a length of 20 mm stretching inwards from just within the outer surface of the liver parenchyma A small portion of the innermost end of the sample was immediately treated for electron microscopic studies as previously described (7)

Submitted for publication March 23 1964

Results

In the alcoholics studied (18 males and 6 females) various amounts of liver mitochondria with abnormal shape, size and ultrastructure were found Sometimes single abnormal mitochindria were scattered among normal ones sometimes many were found together and with a varying degree of the same type of abnormality Giant mitochondria were frequently found and were mainly of two types either swollen, round or angular (fig 1A) or very long and with varying thickness (figs 1B and 2) Single cells could hold numbers of pathologically shaped mitochondria whereas surrounding cells were poor in these types but rich in normal ones (fig 3)

Discussion

A constant stream of cases are reported showing mitochondria more or less deviating from normal as regards shape size and ultrastructure The backgrounds are extremely varied including starvation anoxia intoxications and sev

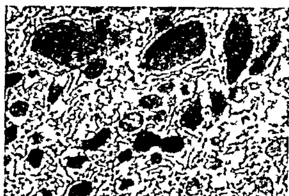


Fig 1A

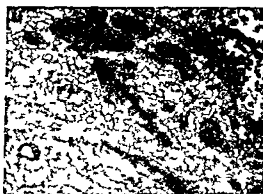


Fig 1B

Fig 1A Mitochondria from a 36-year old man with a periodic drinking pattern Biopsy 6 days after the last alcohol consumption 12 000 ×

Fig 1B Mitochondria from a 49 year old man consuming alcohol daily for many years Biopsy 16 days after the last alcohol consumption 12 000 ×



Fig 2 Mitochondria from a 50 year-old man consuming alcohol for at least 15 years Biopsy at least one month after the last alcohol consumption 30 000 ×

eral natural diseased states For a detailed revue see (8)

Ethanol consumed by rats for a long time has been shown to cause both metabolic and histological disorders in the liver mitochondria (3—7) The material accounted for in the present paper suggests that ethanol in amounts consumed by certain human alcoholics may influence the morphology of their liver mitochondria

In alcohol treated rats a few types of malformations were more frequently seen than others (7) In human liver from alcoholics deviations from normal were seen in many forms Whether some of these were different phases of the same process has still to be established

Giant mitochondria have been described in connection with liver diseases (1 2) and after starvation (8) Livers from human alcoholics also contain abnormally big mitochondria The two types mainly found are seen in figs 1 and 2 In contrast to the round type (fig 1A) the ultrastructure of the long ones consist of many cristae often very tight together and arranged in parallel (fig 2) In several cases the mitochondria contain striped regions (figs 1B 2 and 3) resembling those described in other con

nections by Je/equel (2) and Ekholm and Edlund (1)

M tochondrial degenerat ons lead ng to the format on of ves cles common in l ver from rats treated with ethanol (7) are rare in the l vers of the human alco hol cs stud ed

Fig 4 sho s liver mitochondria from a man three years after cessat on of a heavy alcohol consumption of several years durat on W th ind v dual excep t ons the mitochondr a are of normal shape and size

The abnormal t es described above are *only* a fe v and *the more* eas ly recognizable of the pecul arit es found among the m tochondr a of the human l vers stud ed O ving to the small s ze of the present material no comparison can as yet be made between alcohol c *man* and won an

Us ng human mater al is of course hazardous from *many* po nts *of* v ew The vague informat on about the dr nk ing pattern the irregular consumption of adequate sol d food the possib lity of a s multaneous ab se of other drugs the vary ng ages and states of health are per haps the most outstand ng factors mak ng the mater al all but homogeneous As llustrat ons n th s paper only p c tures have been used from male alcohol cs w th no abuses other than ethanol *thus at least partly* el m nat ng son e of the rrelevant factors

Summary

In humans heav ly abu ng ethyl alcohol l er m tocl ondria th abnormal shape and s ze are frequently found In the present report some of these types are shown



F g 3 M ochondr a f om t e same man as shown in fig 1B 5 000 ×



F g 4 M tochondria f om a 58-year-old man the b opsy aken 3 years af er he ceas ng of a heavy a cohol con umption of several years dura on 9 000 ×

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Intestinal Absorption of ^{45}Ca and Dynamics of ^{45}Ca in Gastrectomy Osteoporosis

By

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A partial gastrectomy may be followed after a few years by an osteoporosis This has been demonstrated radiologically by Bonorino-Udaondo and Castex (3) by Campanacci (4) and by several others

Other authors have observed isolated cases of severe osteomalacia which occurred some time after a partial gastrectomy and which could be influenced favourably by a treatment with vitamin D or with large doses of calcium lactate (2 15) or by reinsertion of the duodenum into the digestive tract (when the gastrectomy had been carried out by the method of Polya (10))

More recently investigations have been made of the metabolism of calcium in patients who have been subjected to gastrectomy

In 1955 Nicolaysen and Ragard (13) were able to demonstrate that the calcium balance is negative in patients who have been gastrectomized

In 1961 Lichtwitz et al (12) observed a low excretion of calcium in the urine and a negative calcium balance, due to defective intestinal absorption They confirmed that bone alterations of the osteoporotic and osteomalacic type are frequently seen in gastrectomized subjects who have been operated on by the method of Polya or by the method of Finsterer (none of those subjected to gastrectomy by the method of Péan have shown alterations of the phosphorus calcium metabolism)

In 1962 Harvald et al (9) proved with the aid of the 'net 12 hour urinary excretion of Ca method of Nordin and Fraser that a latent osteomalacia is very often present in those who have been treated by gastrectomy in many of these authors patients, the intestinal absorption of calcium was markedly deficient In order to throw more light on this problem we have carried out a metabolic study with ^{45}Ca in a group of 12 patients with osteoporosis due to partial gastrectomy in all these patients the gastrectomy had been carried out with a method which excluded the duodenum from the digestive tract

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TABLE I

	Sex	Age	Body weight (kg)	Gastrec since (years)	Intake (mg/24 h)	Stools (mg/24 h)	Urine (mg/24 h)	Balance (mg/24 h)	Intest utilisat (%)	Endog faecal Ca (mg/24 h)
Patients										
P G	♀	73	50	32	1 000	1,000	88	− 88	11 5	115
N A	♂	73	56	14	1,400	1,300	108	− 8	16	139
N L	♂	66	40	11	1,250	1 200	108	− 58	14	132
M O	♂	74	51	5	950	1 000	98	−148	7	120
G G	♀	63	50	15	950	900	91	− 41	17	115
A A	♀	61	57	31	1 100	1 050	103	−153	13	96
F A	♂	36	50	10	800	750	98	− 48	18	98
Normals										
S R	♀	73	80	—	900	700	163	+ 37	32	90
L R	o	35	60	—	980	750	180	+ 50	35	120
*	♂	22	70	—	920	—	180	—	34	120

* Aubert and Milhaud (1960)

Material and methods

1) THE CA BALANCE AND THE UTILIZATION OF INGESTED CALCIUM IN GASTRECTOMY OSTEOPOROSIS

We have studied, from this point of view, 7 patients, ranging in age from 36 to 74 years, who had been subjected to partial gastrectomy from 5 to 32 years previously and who presented a vertebral osteoporosis which could be observed more or less distinctly on the radiogram

1) *Calcium balance* This examination was carried out over a period of 6 days, with determination of the

a) calcium intake The patients were allowed to eat what they wanted but a precisely similar quantity of food was used for the determination of the calcium intake The meals set aside from these six days were mixed, weighed, homogenized and cal cinated, and the quantity of calcium was determined in the end product by the method of Clarke and Collip,

b) faecal calcium The period of the balance study was marked by giving 0 5 g carmine red orally at its beginning and at its end The faeces from the 6 days were then subjected to the same treatment as is described for the food,

c) urinary calcium The urine from these six days was carefully mixed and measured and its calcium content was determined by the method of Clarke and Collip

2) *Utilisation of ingested calcium* This was obtained from the ratio between the calcium absorbed by the intestine (Ia) and the calcium intake (Ii) expressed in mg/24 hrs $\frac{Ia}{Ii}$ 100 The calcium absorbed by the intestine (Ia) was determined by the ⁴⁵Ca method using the following formula

$$I_a = I_f + I_i - F$$

in which

V_f = endogenous faecal calcium mg/24 hr

V = calcium intake mg/24 hr

F = total faecal calcium mg/24 hr

3) *Endogenous faecal calcium* (I_f) This was determined by the ⁴⁵Ca method based on the following principle the specific radioactivity of the urine of the plasma and of the digestive juices is the same at any given moment, therefore

$$I_f = I' \frac{R_f}{R}$$

in which

I' = urinary calcium in mg/24 hr

R_f = total radioactivity of the faeces during the 6 days of the experiment

R = total radioactivity of the urine during the 6 days of the experiment

In agreement with the findings reported by Nicolaysen and Ragard (13) and by Lichtwitz et al (12), in all the 7 cases we have studied the calcium balance was negative by an amount ranging from 8 mg/24 hr to 153 mg/24 hr

As can be seen in table I and fig 1

1) The calcium intake lies within normal limits
2) The urinary calcium level is rather low (from 88 to 108 mg/24 hr)
3) The faecal calcium concentration is very high sometimes higher than the calcium intake

The negativity of the calcium balance is therefore to be attributed directly to the low absorption of calcium from the food

The utilization of ingested calcium was rather low from 7 to 18 % as against normal values of 30 to 40 %

In order to elucidate the significance of the large quantities of calcium excreted with the faeces we determined the endogenous faecal calcium and found it to be within the limits of normal (more precisely, near the lower limit of normal) Apparently the exclusion of the duodenum from the digestive tract and the rapid passage of the food through the intestine (which is so often seen after gastrectomy) do not allow a normal utilization of the calcium in the food

2 Intestinal absorption of ⁴⁵Ca in gastrectomy osteoporosis

Using the method described in a *previous* article (5) we have studied the intestinal

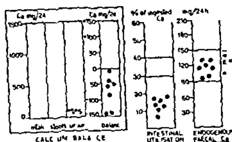


Fig 1 Calcium balance intestinal utilization of ingested Ca and endogenous faecal calcium in 7 cases of osteoporosis due to gastrectomy

absorption of ⁴⁵Ca in 6 cases of osteoporosis due to partial gastrectomy

After oral administration of 50 microcuries of $^{45}CaCl_2$ (dissolved in 10 ml of a solution of calcium gluconate 10 %) we determined

1) the radioactivity in the plasma from blood samples taken every 5 minutes for 30 minutes and then every 30 minutes for 2 hours
2) The radioactivity of the urine collected within the first 6 hours
3) The radioactivity of the faeces collected during the first 72 hours

As can be seen in table II and in fig 2 in the cases of osteoporosis due to gastrectomy we observed

1) an appearance of the radioactivity in the plasma which was later than in the normal subject (from 20 to 30 minutes after the administration of the dose as against 10 to 15 *minutes in the normal subject)*
2) maximal radioactivity values after 60 to 90 minutes which were lower than in the normal subject 1—2 % of the dose per litre of plasma as against values of 2—2 5 % in the normal subject
3) values of the urinary excretion of ⁴⁵Ca lower than in the normal subject (from 0 25 % to 0 62 % of the dose as against values of 0 82 to 1 01 % in the normal subject)
4) higher values of faecal excretion of the ⁴⁵Ca (from 48 to 71 % of the dose as against values of 29 to 38 % of the dose in the normal subjects)

TABLE II

Sex	Age	Gastrec since (years)	Plasma activities % dose/l plasma												Urine (% dose)				Stools (% of dose)
			minutes												hours				
			5	10	15	20	25	30	40	50	60	90	120	210	0—2	2—4	4—6	0—6	0—72 hrs
Patients																			
P G ♀	73	32	—	—	—	—	—	+	30	50	70	90	1 05	83	02	13	10	25	65
N A ♂	74	14	—	—	—	—	+	40	81	1 18	1 50	1 40	1 32	1 11	05	16	.20	41	60
R G ♂	59	9	—	—	—	—	+	51	1 00	1 42	1 60	1 83	1 70	1 52	10	12	20	42	53
C T ♂	56	13	—	—	—	+	78	1 39	1 80	2 11	2 21	2 21	2 10	1 81	20	17	25	62	48
S R ♂	52	3	—	—	—	—	—	+	40	65	80	1 00	95	65	08	11	11	30	71
B N ♀	70	8	—	—	—	—	—	+	51	90	1 10	1 32	1 31	85	12	28	10	50	62
Normals 5 cases (average)			—	+	25	41	71	96	1 52	1 73	2 17	2 37	2 36	2 10	21	35	42	97	33

\+ Small amounts of radioactivity

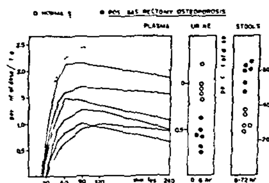


Fig 2 Intestinal absorption of ^{45}Ca in 6 cases of osteoporosis due to gastrectomy and in 5 normal cases

To sum up in our cases of gastric resection, the intestinal absorption of ^{45}Ca was slower and reached lower values than in normal subjects This is directly confirmed by the low renal excretion and by the high faecal excretion of the tracer substance The intestinal absorption of ^{45}Ca appeared to be not greatly impaired in case C T unlike all the other patients, this patient showed no pronounced radiological alterations of the skeleton

3) ^{45}CA DYNAMICS IN GASTRECTOMY OSTEOPOROSIS

From this point of view, we examined the same 7 patients already studied in regard to the calcium balance

The method we have applied was that of Aubert and Milhaud (1) This method is based on the following technique

1) Intravenous injection of 5 microcuries of ^{45}CaCl ,
2) Determination of the specific radioactivity of the serum calcium of the total radioactivity of the urine and of the faeces, and quantitative determination of the calcium ingested and excreted
3) Mathematical analysis of the curve of the decrease of the specific radioactivity of the serum calcium Between the 48th hour and the 6th day this curve follows an exponential function and can be expressed with the following formula

$$SA_t = SA_0 e - kt$$

in which

SA_t = specific activity at time t

SA_0 = specific activity at time zero which

TABLE III

	Sex	Age	Body weight (kg)	Gastrectomy since (years)	Miscible pool (mg/kg)	Turnover rate (mg/h)	Accret rate (mg) kg/24 h)	Resorpt rate (mg) kg/24 h)
Patients								
P G	♀	73	50	32	250	102	45 1	46 8
N A.	♀	73	56	14	260	116	45 6	45 7
N L.	♂	66	40	11	250	104	56 4	57 8
M O	♂	74	51	5	225	73	30 3	33 2
C G	♀	63	50	15	205	57	23 4	24 2
A A	♀	61	57	31	155	88	33 8	36 6
F A	♂	36	50	10	200	96	42 1	43 1
Normals								
S P	♀	73	80	—	77	53	12 6	12 0
L. R	♂	35	60	—	103	43	12 3	11 5
*	♂	22	70	—	93	46	12 5	12 4

* Aubert and Milhaud (1960)

can be found by extrapolating the curve to the zero point

e = base of natural logarithms

k – fractional turnover rate $k = \ln 0.5/T_{1/2}$, $T_{1/2}$ being the half time of the curve

The radiochemical quantitative determinations have been carried out with the method described in our previous communication (5) the quantitative chemical determinations of the calcium have been carried out with the method described above

Using this method we have calculated the following values

1) calcium miscible pool (P) $P = \dfrac{R_1}{SA}$

in which

R_1 injected radioactivity

SA = the extrapolation value of the curve at zero time

2) calcium turnover rate (V_t) $V_t = k\,P$

3) accretion rate (V_a) $V_a = V_t - (V_f + V_u)$

in which

V_f endogenous faecal calcium mg/24 hr

V_u urinary calcium mg/24 hr

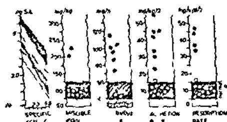


Fig 3 ⁴⁵Ca dynamics in gastrectomy osteoporosis (●) and in senile osteoporosis (○)

4) resorption rate (V_o) during the 6 days of the experiment the calcium miscible pool (P) was practically constant so that the quantity of calcium which is added to the pool (calcium absorbed from the intestine V_a and the calcium derived from the bone V_o) is the same as the quantity that leaves the pool (faecal calcium urinary calcium and bone accretion) and therefore $V_a + V_o = V_t$ but the total calcium of the faeces (F) is $F = V_f + V_t - V_a$, so that the resorption rate (V_o) can be calculated with the following formula $V_o = V_t - (V_f + V_u - F)$

Conclusions

1) *Calcium miscible pool*

The values that we have found were always above the normal range they were between 155 4 and 260 mg/kg, as against normal values of 75 to 125 mg/kg In other words, in the skeleton of gastrectomized patients with osteoporosis, there are extensive zones that have a rapid calcium turnover, which explains the high value of the calcium miscible pool

2) *Calcium turnover rate*

With only one exception, the values we have found in gastrectomized subjects with osteoporosis were much above the normal range To be exact, in the gastrectomized subjects the calcium turnover rate varied between 57 4 and 116 4 mg/hour, as against normal values of 40 to 60 mg/hour

3) *Accretion rate*

The values we have found in the gastrectomized subjects with osteoporo is were much above the normal range, viz from 23 4 to 56 4 mg/kg/24 hours, as against a normal range of 5 to 15 mg/kg/24hours

This fact constitutes an indirect pointer to the quantity of calcium which tends to be fixed stably into the skeleton therefore, there is some evidence indicating that in gastrectomized subjects there is an intensive neoformation of bone

4) *Resorption rate*

The values we have found in gastrectomized subjects with osteoporosis are above the normal range they lay between 24 2 and 57 8 mg/kg/24 hours as against normal values of 5 to 15 mg/kg/24 hours

In the individual cases, the resorption rate was always above the excretion rate in other words, there is not only an intensive process of bone accretion, but also an even more intensive process of resorption of the bone

It is of particular interest to compare the variations of the dynamics of ^{45}Ca in osteoporosis due to gastrectomy with those that can be observed in senile osteoporosis (fig 3)

The dynamics of ^{45}Ca in senile osteoporosis we have discussed elsewhere (7, 11)

In senile osteoporosis the calcium miscible pool, the excretion rate, and the resorption rate are almost always within the limits of normal The calcium turnover rate, on the other hand, is practically always below normal

In other words, the ^{45}Ca dynamics in osteoporosis due to gastrectomy differs completely from that in senile osteoporosis

This difference becomes even more significant if we take into consideration that many of our gastrectomized subjects were of advanced age

The ^{45}Ca dynamics in osteoporosis due to gastrectomy is similar to that in osteomalacia The osseous zones with rapid calcium turnover are larger than in the normal subject, and the rhythm of excretion and reabsorption is intensified

A histological biopsy study of the bone from the iliac crest (6), which was carried out in 4 of our cases, led to the conclusion that in all these subjects there was a considerable degree of osteoporosis, and two of them showed distinct osteoid seams around the trabeculae of the spongy bone, in accordance with the findings obtained by Lichtwitz et al (12), by Nitschke and Giegler (14) and by Hall and Neale (8)

However the histological changes in osteoporosis due to gastrectomy are not the same as those that are characteristic of osteomalacia the osteoid seams are present but the bone trabeculae are extremely thin and scarce just as is seen in osteoporosis In other words, the picture is that of a mixed osteoporosis and osteomalacia (osteoporomalacia)

Summary

In 7 cases of osteoporosis after partial gastrectomy, the intestinal absorption of ^{45}Ca was found to be delayed and decreased, in these same cases, the calcium balance was always found to be negative as the result of deficient utilization of the calcium from the food

In 6 other cases of osteoporosis due to gastrectomy, a study was made of the ^{45}Ca dynamics The calcium miscible pool the calcium turnover rate, the accretion rate and the resorption rate all were found to be constantly increased This is due to the excessive availability of incompletely mineralized bone, which disposes to a rapid turnover of the radiocalcium as the result of an intensive osteoblastic and osteoclastic activity

The histological study of 4 cases led to the conclusion that there exists a mixed condition of osteoporosis and of osteomalacia

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Granulocyte Precursor Generation Times as Derived from the Total Granulocyte Turnover Rate[1]

By

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To understand the nature of pancytopenia and leukemia information about the growth rate of granulocyte precursors is essential In the present study, an attempt is made to calculate granulocyte precursor generation times (t) using available data on the total number and distribution of the bone marrow cells, and on the total granulocyte turnover rate

Method and results

Details of the method and mathematical derivation, necessary assumptions, and estimates of the total number of bone-marrow cells have been published (9) The normal distribution of bone marrow cells has been given (1), and thus the total number of different granulocyte precursors can be deduced (table I) The total granulocyte turnover defined as the number turned over through the blood each day has been estimated to be 179 9 ± 74 3 × 10⁷ cell per kg of body weight (3) or 10 8 × 10¹⁰ cells/day in a 60 kg man If it is assumed (3) that granulocytes do not return to the blood or bone marrow from the tissues and if all metamyelocytes enter the blood as granulocytes, this number must be equal to the number of metamyelocytes produced by the myelocytes, E_s According to the previously given equations (equation numbers in brackets refer to ref 9), and to previous assumptions (9)

$$\text{(Eq 6)} \quad t_M = \frac{2\, N_M}{E_s} = 1\ 61 \text{ days}$$

$$\text{(Eq 10)} \quad t_P = \frac{2\, N_P\ t_M}{N_M} = 1\ 11 \text{ days}$$

$$\text{(Eq 11)} \quad t_B = \frac{N_B\ t_P}{N_P} = 0\ 44 \text{ days}$$

Discussion

Previous estimates of these generation times are given in table II The present calculated values agree reasonably well with figures obtained with the stathmo-

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[1] Paper given in Svenska Läkarsällskapet Jan 21 1964

TABLE I Estimated total number of granulocyte precursors in a 60 kg man

Morphological description	Symbol	Total No (ref 1 and 9)
Myeloblasts	B	$N_B = 12 \times 10^9$
Promyelocytes	P	$N_P = 30 \times 10^9$
Myelocytes	M	$N_M = 87 \times 10^9$
Metamyelocytes	S	$N_S = 110 \times 10^9$

kinetic method, but are shorter than those obtained from mitotic indices, assuming a mitotic time of one hour

The stathmokinetic method itself (2) gives only relative proliferation rates, but these can be compared with those obtained by the present method (9) This is done in table III, and a satisfactory agreement is found

TABLE II Estimates of human leukocyte precursor generation times

	Generation time (hours)			
Author	Method	t_B	t_P	t_M
Journoud (7)	Astaldi s figures (2)	15 2	18 3	
Cronkite et al (6)	H³ thymidine		Average 30 hours	
Killman et al (8)	Mitotic indices	19 8—39 7	33 5—44 6	58 3—64 1
Present paper	Granulocyte turnover rate	11	27	39

TABLE III Ratios between generation times according to stathmokinetic indices (S I) (2) and to present type (T) of calculation (9)

Variable	Method of study	Erythrocyte precursors (9) P	Erythrocyte precursors (9) B	Erythrocyte precursors (9) M	Leukocyte precursors[2] B	Leukocyte precursors[2] P	Leukocyte precursors[2] M
Generation times (9)		4	4	26	11	27	39
S I ‰ (2)		—	200	65—70	128 1	52 6	26 9
Relative generation times Multiples of time for proerythroblasts (t_p)	T	t_p	$2t_p$	$3\ 2t_p$	$2\ 7t_p$	$6\ 8t_p$	$9\ 7t_p$
	S I	—	[1]$2t_p$	$3\ 0t_p$	$3\ 1t_p$	$7\ 6t_p$	$14\ 9t_p$

[1] Assuming S I for proerythroblasts = 400 $t \sim \frac{1}{S\ I}$

[2] For explanation of cell type abbreviations, see ref 9 and table I

The radiosensitivity of granulocyte precursors (6) and the present generation times agree with the "law of Bergonie and Tribondeau" (4)

Most of the assumptions have been discussed (9), that of a single mitosis in each morphologically recognizable stage is supported by the values for the ratio between N s (10) Relationships between times obtained by the present method and those obtained by other methods are the best indications of which of several possible bone marrow models (number of divisions and their localizations in morphological compartments) is the most realistic one

Summary

Tentative generation times for myeloblasts (11 hours) promyelocytes (27 hours) and myelocytes (39 hours) are calculated

Acknowledgement

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B_{12} Lack ("Pernicious Anaemia"), Possibly Caused by "Parasitization" (Consumption by a Neoplasm), in a Case of Waldenstrom's Macroglobulinaemia

By

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Some degree of normochromic or hypochromic anaemia is often seen in Waldenstrom s macroglobulinaemia (8), it is sometimes caused by mucosal bleeding or by replacement of bone marrow by abnormal lymphoid cells, and rarely by abnormal haemolysis (12) In the case of Waldenstrom s disease to be described below anaemia was caused by cobalamin deficiency we suggest that this deficiency was a consequence of tumour growth

Methods

Free electrophoresis was performed in the Perkin Elmer apparatus type 38 with a Schlieren scanning device (courtesy of Mr S K Wadman Ph D Biochemical Laboratory Zuiderziekenhuis)

Ultracentrifugation was carried out in a Spinco-E ultracentrifuge with Schlieren scanning device (courtesy of Mr P F Mijnheff Ph D van t Hoff Laboratory Utrecht)

Immuno-electrophoresis was done according to Scheidegger s (17) microtechnique in the modification of Wieme (23)

Serum cyanocobalamin levels were determined with the use of Lactobacillus leichmannii A.T C.C. 7830 (courtesy of Mr J A de Vries Microbiological Laboratory of Philips-Duphar Ltd Weesp) normal levels are between 300 and 1000 $\mu\mu g/ml$

Schilling tests were done with a test dose of 1 μg of ' Co-cyanocobalamin with a radioactivity of 0 4 μC flush doses of 1 mg each, given at 2 and at 24 hours after the test dose and collection of urine during 48 hours normal excretion is between 13 and 48 % (courtesy of Mr W Schopman Ph D Biochemical Laboratory of the Bergweg Ziekenhuis Rotterdam)

Case report

A woman aged 86 was admitted to the medical ward of the Zuiderziekenhuis on Nov 8 1960 because of pneumococcal pneumonia she soon recovered through treatment with *penicillin* In addition examination revealed anaemia slight jaundice hypertension (210/130 mm mercury) with enlarged heart and a kyphotic dorsal spine which was painful on percussion and on moving

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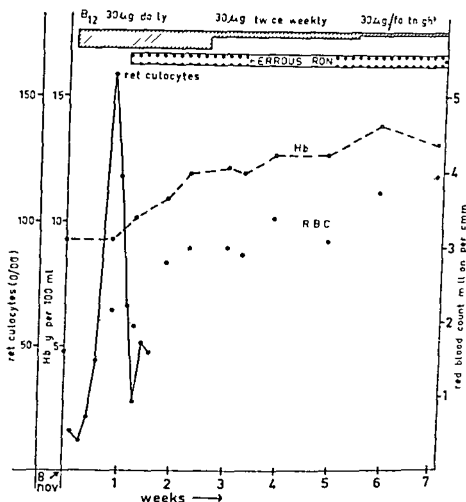


Fig 1 Response of reticulocytes red blood count and haemoglobin to treatment with cyanocobalamin (and iron

Routine laboratory studies

The urine contained a trace of protein and much urobilin E S R was 141 mm in the first hour (Westergren) Hb was 9 3 g/100 ml White cell count during pneumonia 21 000 mm³, afterwards 5900 mm³ with normal differential count Serum bilirubin was 3 0 mg/100 ml alkaline phosphatase 8 1 King Armstrong units, thymol turbidity 8 4 Mc Lagan units serum gammaglobulin 3 1 g/100 ml (ammonium sulphate turbidity) serum glutamic-oxalacetic transaminase 43 Wroblebski units glutamic pyruvic transaminase 18 units, blood urea 84 later 36 mg/100 ml, serum creatinine 1 45 and 0 9 mg/100 ml respectively

Haematological investigations

Hb 9 3 g/100 ml, red cell count 1 6 mill/mm³ mean diameter of red cells in the slide 9 6 µ reticulocytes 1 6 % platelets 210 000/mm³ (direct count) Red cells showed marked anisocytosis and poikilocytosis Serum iron 122 µg/100 ml unsaturated binding capacity 100 µg/100 ml Bleeding time 2 minutes (Duke) prothrombin time 15 seconds (normal control 15 seconds) Thromboelastography normal

Sternal marrow obtained immediately after admission (Nov 9) showed typical hyperplastic megaloblastic erythropoiesis and many giant stabs In addition plasma cells appeared to be increased Consecutive bone

marrow biopsies on Nov 24 (after institution of treatment with parenteral cyanocobal amin) on Aug 3 1961 and on Nov 16 1961 revealed apart from a normoblastic erythropoiesis the presence of plasma cells in increasing amounts These plasma cells were distinctly smaller than and the chromatin was much more disperse than that of normal plasma cells there was no clumping of the chromatin The cells were considered to be neoplastic

Cyanocobalamin economy

Serum cyanocobalamin level was 50 $\mu\mu$g/ml There was histaminerefractory gastric achylia Loss of fat and fatty acids with the stools was 0 7 and 0 8 g per 24 hours respectively After an oral dose of 25 g d xylose 3 9 g was excreted in the urine in five hours (normally 4 g or more)

We twice did a Schilling test from Nov 22 to 24 1960 and from August 29 to 31 1961 The first time 17 % the second time 20 % of the test dose was excreted in the urine in 48 hours There was no diarrhoea faecal contamination could be excluded Thus the results were clearly normal

Response of anaemia to treatment with vitamin B_{12}

On Nov 9 1960 treatment with cyanocobalamin was started with daily intramuscular injections of 30 μg The results were as might be expected in cyanocobalamin deficiency (fig 1) In addition to the data in fig 1 serum iron fell to 67 μg/100 ml within two days and serum bilirubin became normal (0 7 mg/100 ml)

Study of serum proteins

Total serum protein content was 7 3 g/100 ml (Kjeldahl) Free electrophoresis albumin 2 6 α_1-globulins 0 6 α globulins 0 6 β globulins 0 9 γ globulins 0 2 γ_1-globulins 2 4 g/100 ml The γ_1 peak was very high and had a narrow base (fig 2) this suggested the presence of a paraprotein

Paper electrophoresis after electrophoretic separation of the fractions paper strips were treated with appropriate techniques which

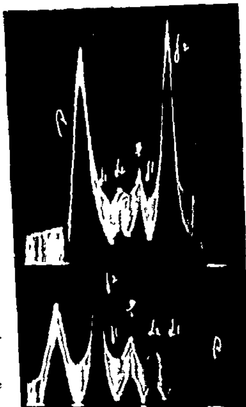


Fig 2 Free electrophoresis of serum

showed the presence in the γ_1 region of carbohydrate (PAS) lipid (sudan black) and nucleoproteins (pyronin methyl green) Cryoglobulins were absent

Ultracentrifugation showed the presence of a pathological macroglobulin with sedimentation constant (S20) of 15 9 S (fig 3) In the agar gel electrophoresis experiment the pathological protein did not migrate but showed a zone of precipitation on the cathode side of the well into which the serum was placed Immuno-electrophoresis with anti β_M serum (Behring Werke) revealed the presence of an abnormal precipitation zone in the same region and additionally a minute precipitation zone probably corresponding to normal β_2 macroglobulin (fig 4) After treatment of the serum with cysteine HCl in a phosphate buffer (Burtin 1) at 0 centigrade

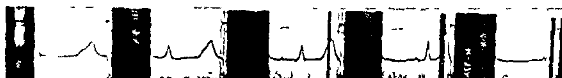


Fig 3 Ultracentrifuge diagram of serum Pictures from right to left were taken at 5 15, 25, 35 and 45 minutes respectively after the apparatus had reached 60,000 rotations per minute A sharp peak of abnormal macroglobulin *is seen to the* right of the small peak representing physiological macroglobulins



Fig 4 Immuno-electrophoresis diagram, cathode to the right Above patient below normal *control Anti* β_2*M serum (Behring Werke)*

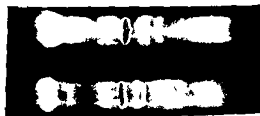


Fig 5 Agar gel electrophoresis diagram Albumin to the left Above normal control below the patient s serum treated with cysteine HCl at 0° C Precipitation in the β zone

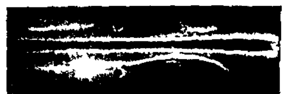


Fig 6 Immuno-electrophoresis diagram Above *normal control Below* the patient s serum *treated with cysteine HCl* at 0 centigrade Anti β_2M serum



Fig 7 Immuno electrophoresis diagram Above normal control Below the patient s serum treated with cysteine HCl at room temperature Anti β_2M serum



Fig 8 Ultracentrifuge diagram of patient s serum treated with cysteine HCl at 0° centigrade The abnormal peak of fig 3 has disappeared

during 24 hours, the paraprotein was apparently dissociated into three fractions one of which precipitated in the β_1 region and two produced distinct zones in the β_2 region (fig 5), immuno electrophoresis showed the presence of great quantities of a substance similar in antigenicity to normal β_2M globulin (fig 6) When treatment with cysteine HCl was repeated at room temperature, part of the paraprotein was apparently left intact, so that the precipitation zones of both fig 4 and fig 6 were visible (fig 7)

Ultracentrifugation after treatment with cysteine HCl at 0° centigrade showed disappearance of the abnormal macroglobulin (fig 8)

Calcium metabolism

Serum calcium 9 8 mg/100 ml

Inorganic phosphorus 3 9 mg/100 ml

Urinary calcium excretion was 73, 89 and 152 mg per 24 hours on consecutive days while calcium intake was low

X ray examinations

X ray films of the chest revealed a left lower lobe pneumonia disappearing on follow up The heart was enlarged to the left The spine showed extreme decalcification with fish vertebrae in the lumbar region and pathological fractures of the ninth eleventh and twelfth dorsal vertebrae Skull and pelvis also showed diffuse decalcification

Discussion

The serum protein abnormalities mentioned above fit a diagnosis of Waldenstrom's macroglobulinaemia Although bone marrow examinations did not reveal an abnormal proliferation of lymphoid reticulum cells or an increase in basophil mast cells there was an unequivocal proliferation of atypical plasma cells this has been formerly described by several authors (9, 27) as the sole cytological sign in certain cases of Waldenstrom's macroglobulinaemia

The severe osteoporosis occurring in our patient, with spontaneous fractures of several vertebrae probably may be regarded as a manifestation of macroglobulinaemia (8) Recurrent respiratory infections often occur in macroglobulinaemia (8) as well as in multiple myeloma In particular pneumococcal pneumonia has been frequently described in the latter condition (18) a decreased ability to form specific antibodies (26) being held responsible The pneumonia in our patient was possibly promoted by the same mechanism

In addition to macroglobulinaemia there was definite evidence of vit B_{12} deficiency in our patient (megaloblastic anaemia low serum vit B_{12} level typical response to parenteral cyanocobalamin in moderate doses (fig 1) The cause of this B_{12} deficiency is not self evident B_{12}-deficiency may firstly have a gastrointestinal cause, secondly there may have been insufficient dietary intake, and thirdly, it is seen in conditions to be discussed below, where its occurrence is less well understood

Possible gastro-intestinal causes are absence of intrinsic factor, disease of the gut with malabsorption syndrome, and destruction by tape worms or bacteria These conditions can be ruled out in the case of our patient, for there was no malabsorption syndrome and above all, the Schilling test was repeatedly normal

Megaloblastic anaemia caused by insufficient dietary intake of cyanocobalamin is extremely rare in temperate climates (2, 3, 5, 7, 24) Almost all patients described were food faddists or very strict vegetarians, mostly vegans they were much younger than our patient (3 6 19, 20 22) Moreover, cyanocobalamin deficiency in such cases usually causes combined degeneration of the spinal cord rather than anaemia (5 25) possibly a normal intake of folic acid prevents anaemia

A crucial point in the judgment of our case is whether the diet of our patient had been deficient in cyanocobalamin She was an old crippled woman living alone But with the aid of a granddaughter she kept her household very well as we convinced ourselves by paying her a visit after her discharge from hospital Our dietician took a dietary anamnesis Food intake had been near normal she ate meat three to four times weekly and drank milk daily Both milk and especially meat are

sources of cyanocobalamin. Her intake of cyanocobalamin was thus estimated to have been sufficient — though perhaps not liberal — by our dietician.

A third group of causes of cyanocobalamin deficiency is described by Herbert (7) as "inadequate utilization". In this group figure patients who lacked the vitamin B_{12} binding protein in the serum. Such patients do not response to intramuscular cyanocobalamin therapy. As our patient did improve after such therapy, we can rule out this possibility in our case.

But under the same head figure cases which are more like ours. For this cause of deficiency Herbert coined the word "parasitization". By this term he means that a rapidly growing tissue consumes so much of a vitamin that the patient suffers from deficiency, despite a dietary intake and intestinal absorption which would otherwise have been adequate. Examples of such rapidly growing tissues are a foetus, malignancy, or erythroblasts in haemolytic anaemia, and Herbert accepts the three of them as causes of megaloblastic anaemia and as instances of "folic acid deficiency by parasitization", whereas only pregnancy is accepted as a cause of "cyanocobalamin deficiency by parasitization".

There are reasons to believe that likewise new growths, at least of plasma cells, can induce cyanocobalamin deficiency by this mechanism. Both Mandema (13, 14) and Larsson (11) found low levels of cyanocobalamin in the blood serum of patients with multiple myeloma. Killander and Larsson (10) studied cyanocobalamin absorption by the Schilling test in cases of myeloma. Results were normal even in a patient whose serum level of cyanocobalamin was 51 $\mu\mu$g/ml. Both Mandema (13) and Larsson (11) suggest as a possible cause of these low levels consumption of vitamin B_{12} by the abnormal plasma cells, but neither of these authors saw megaloblastic changes in the bone marrow, nor did the anaemia of the patient of Killander and Larsson (10) respond to treatment with cyanocobalamin. However, megaloblastic changes and occurrence of giant stabs in the bone marrow have been described by other authors (16, 24). Waldenström's macroglobulinaemia, though a completely separate disease, is closely related to myeloma and the cells proliferating in the bone marrow may be very similar to plasma cells (9, 27). It is reasonable to suppose that what applies to cyanocobalamin consumption in myeloma also holds for macroglobulinaemia. Endtz (4) described a patient with macroglobulinaemia and "polyneuritis carcinomatosa". This polyneuritis he ascribed to consumption of vitamin B_1 by the proliferating lymphoid cells — another possible instance of "deficiency by parasitization".

There are other reasons for supposing that plasma cells consume vitamin B_{12}. Recently the occurrence of reversible hypogammaglobulinaemia in pernicious anaemia was described (21), gamma globulin rose after treatment with cyanocobalamin. The most likely explanation seemed to be that plasma cells need vitamin B_{12} for their growth and function, i.e. production of antibodies = gamma globulins. One may ask why cases similar to ours have not been earlier described

But one should not forget that we should have considered our case as simply pernicious anaemia if we had not performed electrophoresis and a Schilling test The Schilling test in particular is an expensive procedure and only recently available, it may easily be considered superfluous, as ours seemed to be

We are, then, led to suppose that "pernicious anaemia in our patient was caused by the fact that she consumed a modest, perhaps border line amount of cyanocobalamin in her diet — a quantity that would have prevented the occurrence of megaloblastic anaemia, had not part or most of this quantity been consumed by macroglobulinaemia cells

We are fully aware that we have not proved our point We have not demonstrated increased turnover of cyanocobalamin in our patient as might have been possible by the technique of Rama Rao et al (15) We have not demonstrated that pernicious anaemia in our patient was cured by taking away her cyanocobalamin consuming new growth without changing her diet — the former being an impossible task Our observation is an isolated one But we are afraid that the life of a clinician is too short to repeat our observation We feel justified in inviting others to repeat it only thus can our supposition be proved

Summary

It is argued that typical cyanocobalamin deficiency with megaloblastic anaemia in a woman aged 86 was probably due not to faulty resorption (results of Schilling s test were normal), nor to severely insufficient dietary intake, but to consumption of the vitamin by a plasmacellular neoplasia with Waldenström s macroglobulinaemia

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The Occurrence of Serological "Antibody" Reagins or Similar γ-Globulins in Conditions with Monoclonal Hypergammaglobulinemia, such as Myeloma, Macroglobulinemia etc

By

Jan Waldenstrom Sten Winblad, Jan Hallén and Sigbritt Liungman

Our understanding of the pathology in myeloma, and in similar conditions with an increase in so-called M components among the gammaglobulins would be greatly advanced if we could decide whether this increased globulin is chemically abnormal — i a so called para protein — or whether it is one of the normally occurring gammaglobulins and is increased only in quantity We have reason to believe that the hypergammaglobulinemia seen in these conditions is caused by increased formation of one (or possibly some closely related) individual gammaglobulin(s) Burnet (1) has interpreted this as indicating a clonal proliferation of one mutated plasma cell that was the origin of all myeloma cells in that patient One of the present authors (J W) has therefore suggested the expression monoclonal hyperglobulinemia for all conditions with M components (13) The expression obviously retains its meaning even if the proliferation is caused not by a mutation but by some other more physiological process as seems more probable The term M component was introduced by Riva (11) for high peak (in free electrophoresis) or narrow band (in paper electrophoresis), globulin fractions The letter M was selected because it could mean both myeloma and macroglobulinemia It could of course also be short for monoclonal! In this paper γ_G (γ) means γ by immunoelectrophoresis and in many instances it was also defined as a 7 S component in the ultracentrifuge, $\gamma_A(\gamma_{1A}) = \beta_{2A}$ immunoelectrophoretically and γ_M (γ_{1M}) = β_{M} by immunoelectrophoresis In both these groups sedimentation constants were often determined in the ultracentrifuge For individual data see Heremans Laurell Waldenstrom a o

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(6) We are very grateful to Dr R Bachmann, who gave us data from immunoelectrophoretic examination of a number of our last patients

If some of these M-components were to show resemblances to other well-known members of the gamma (antibody) globulin family, this might support the opinion that they are normally occurring proteins It is already known that some macroglobulin M-components act as cold agglutinins and are in this respect similar to the cold agglutinin occurring in atypical pneumonia

Another problem in this connection is the immunoparesis that seems to be so common in many patients with this type of hypergammaglobulinemia One approach would be to examine the serological pattern, in a number of such sera, for any signs of a suppression of the formation of those common antibody molecules corresponding to the hypogammaglobulinemia that charcteristically accompanies the monoclonal hypergammaglobulinemia

These two questions 1) specific activity of an M component as a serological reagin, 2) low incidence of pathological titers of common serological reagins in patients with M-components, will be treated in the following paper The situation in liver cirrhosis has been reported recently (15) A paper on what we call extensive serology in polyclonal hypergammaglobulinemia is being prepared

Material and methods

The clinical material comprises 188 patients whose sera were shown to contain an M-component on paper electrophoresis All the 31 cases with γ_M component were collected under the heading macroglobulins The mean age in this group was 66 years, the same as in the myeoloma group of 94 patients The group essential benign monoclonal hyperglobulinemia contain all the cases (63) with M-components belonging to the γG or γA types but with no signs of myeloma during a considerable observation period (skeletal destruction, typical bone marrow findings) The mean age in this group was 67 years As controls we have used sera without M components from 42 persons Of these 35 were married to patients with disseminated lupus and 7 were relatives with normal gammaglobulins of patients with hypogammaglobulinemia All the patients in the control group were above 50 and the mean age was 63

Syphilitic serology The classical methods were used Complement fixation against cardiolipin as well as Meinicke and Kline reactions with a cardiolipin antigen were used The antigens were furnished by the State Laboratory of Bacteriology in Stockholm

Anticomplementary activity was determined on fresh sera

The gonococcus complement fixation reaction was performed with an antigen prepared from five different strains after ultrasonic treatment

Bacterial agglutinins against Salmonella typhi 0 and H, Salmonella paratyphi B 0 and H, in suspension free from phenol manufactured by the abovementioned laboratory In many sera the agglutination of Pasteurella tularensis and of Proteus X 19 was determined likewise with antigens from that laboratory Brucella abortus Bang was obtained from the Bacteriological laboratory of the Agricultural Institute in Malmo

Cold agglutinins were determined with human 0 erythrocytes after treatment of the corpuscles at 37° C in order to remove autoagglutinins Heterophilic agglutinins (Paul Bunnel reaction) and hemolysins against ox blood erythrocytes were determined according to Eriksson (4)

Three different methods were used for demonstration of the rheuma factors Waaler

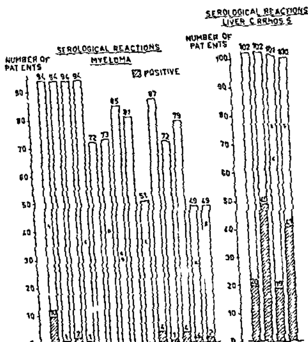


Fig 1

Rose reaction acryl fixation test and F II A reaction with the precipitation technique (17) The acryl fixation test was used instead of the latex fixation test The reactant γ globulin was pooled fraction II from KABI (Stockholm)

Antistaphylolysin was determined with the technic worked out by Ingelstad and Winblad (8) Values above 2 5 units were regarded as positive

Antistreptolysin was measured with a technic used by the same authors Values from 210 to 250 units were regarded as borderline and above 300 as positive

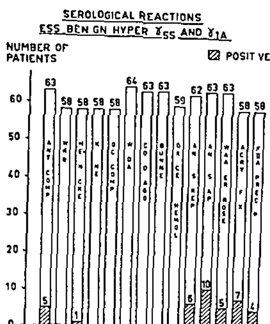
Results

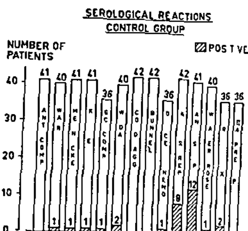
The results of the serological investigation of sera from the control group and the three groups with M components are seen in figs 1 and 2 In tables I—III the results for certain serological reactions in the different groups are compared

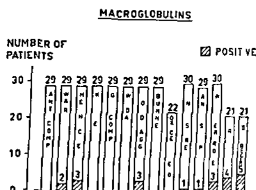
Macroglobulins

There are 31 sera in our material containing an M component with macroglobulin (γ_M) characteristics

Interestingly enough one serum showed strongly positive *Wassermann* (WaR) (480) Meinicke and Kahn reactions The patient G A had no history of syphilitic infection It is regrettable that no TPI reaction was performed at that time A cryoglobulin was present The macroglobulin content of the whole serum was low This patient showed an *acute* leukemic picture but there was a rapid response to Busulphan with a remission that lasted about 2 years The patients died in a relapse Bone marrow slides from punctures were seen by several competent hematologists It was first thought that the round cells







Fg 2

were myeloblasts but Moeschlın with whom we also discussed the slides, was of the opinion that the cells were really reticulum cells The post mortem dis closed a perirenal tumor mass which the pathologists regarded as most closely re sembling granuloma tissue in Hodgkin s disease

It is probable that this patient s macroglobulin increase should be re garded as secondary to the proliferation of the round cells which completely dominated the bone marrow picture This observation shows one of the many tran sitional processes between the well re cognized clinical diseases arising from unlimited proliferation of so called re ticulum cells or their offspring For a discussion of these problems see Walden strom (1962 fig 11 case G A)

Another patient suffered from typical chronic lymphatic leukemia (125 000 W B C/mm³, 93 % lymphocytes 3—4 mill R B C splenomegaly and en larged lymph glands) that first ran a benign course 22 months after the diagnosis the patient died from cachexia with enlargement of lymph glands and palpable abdominal tumors No post mortem was allowed During the last stage after initial hypogammaglobulin emia his serum contained a very small M component that was found to be a macroglobulin Serological examina

TABLE I

Reaction	Macroglobulins		Control		Significance level[1]
	No of cases	Positive (%)	No of cases	Positive (%)	
Cold aggl	29	10	36	0	–
AST	30	3	42	20	*
ASTA	28	1	41	29	*
Rheuma factors					
Waaler Rose	30	10	40	3	–
Acryl fix test	21	19	36	6	–
F II A precip	21	24	36	0	**

[1] P < 0 001 = *** 0 001 < P < 0 01 = ** 0 01 < P < 0 05 = * 0 05 < P = –

TABLE II

Reaction	Myeloma		Control		Significance level[1]
	No of cases	Positive (%)	No of cases	Positive (%)	
Ac	94	11	42	0	
AST	87	5	42	19	*
ASTA	72	1	41	29	***

[1] Symbols as in table I

TABLE III

Reaction	Essential hypergammaglobulinemia		Control		Significance level[1]
	No of cases	Positive (%)	No of cases	Positive (%)	
Ac	63	8	42	0	–
AST	62	10	42	19	–
ASTA	65	16	41	29	–
Rheuma factors					
Waaler Rose	63	8	40	3	
Acryl fix test	58	12	36	6	–
F II A precip	58	7	36	0	–

Symbols as in table I

tion showed a positive WaR (120), and Meinicke, but negative Kline reaction on several occasions TPI was always negative The serum was sometimes weakly anticomplementary (1/15) before any band had developed On one occasion it showed positive acryl fixation test *in a high titer* and also a positive F II A reaction but negative Waaler-Rose No signs of rheumatoid arthritis On this occasion he also had a slight increase in cold agglutinins to a borderline value (1/20) Coomb's test was first negative and later direct 1/32 when the cold agglutinin was slightly positive

There was an M-component of a macroglobulin nature in one other patient, with a hematological picture clinically ill defined, where the post-mortem gave no help On one occasion he had a positive antistreptolysin titer (1/425) that later came down to a borderline value *(1/250)* and was probably caused by a streptococcal in*fection He had no very marked increase* in macroglobulins and started in Nov 1957 *with a polyclonal* γ *1 8 g/100* ml and a β band 1 0 g/100 ml At the same time Kahn reaction was strongly positive The serology was re examined in Jan 1958 At this time the Kahn was still positive as well as the Meinicke reaction WaR was negative on both occasions TPI was negative The bone marrow contained reticulum cells in increased number

The patients that have been discussed so far are all instances of blood diseases that are probably the cause of the very moderate *'symptomatic" increase in* macroglobulins There are two other types of patients *that deserve* special interest

The first consists of a small group of cases, admitted *with hemolytic anemia*, where the presence of macroglobulins in the serum was detected *secondarily to* the demonstration of cold agglutinins It now seems that these high titer *cold agglutinins* are invariably macroglobulins (2, 5) We have observed three patients with a marked increase in macroglobulins (max 1,6 g/100 ml) and very high titers of cold agglutinin Two patients were quite old (man born in 1887, woman born in 1873) In the woman the macro globulin content has kept remarkably constant (about 1,3 g/100 ml) for several years, the cold agglutinin titer 1/325,680 —1/2,621,440 The anemia has kept so constant that we have refrained from treating with cytostatic drugs, fearing that therapy may be more hazardous than the disease itself The man (cold agglutinin titer 1/32,000) had increasing macroglobulin *values (0 65—2 39 g/* 100 ml) He was treated with Melphalan *and his* γ_M *decreased* There was no improvement, however, in his hemolytic status *After 2 1/ months'* treatment he suffered a fracture of the femoral neck and died in an old people's home There was no post mortem

The second group consists of what we have called essential monoclonal hypergammaglobulinemia with all degrees of increase in macroglobulins We believe that no sharp distinction can be made between benign constant macroglobulin emia and malignant progessive macro globulinemia, as the condition may remain stationary for many years and then *ultimately* become fatal We still do not know if there is always an initial benign stage, lasting longer in some pa

tients than in others Instances of an initially benign course with later progression at a rapid rate to a picture of progressive macroglobulinemia have been observed by us There is no reason to believe that these patients have macroglobulins of a special kind, and we have therefore put them all together into one group in discussing the serology

The serological findings in this group of more or less essential macroglobulinemia are surprisingly poor

None of these sera was *anticomblementary*

No sera contained *gonococcal reagins*

Our search for *bacterial antibodies (Widal)* in the 29 sera tested has been without result

The cold agglutinins have already been discussed in the two patients with a high titer One other patient who had a rather atypical clinical picture had a high content of macroglobulins and also some increase in cold agglutinins (1/40) We wish we had saved more of his serum for closer analysis This patient only stayed in the clinic for a short time It is of course theoretically important to know whether all his macroglobulin molecules had some (but very low) action as cold agglutinins or whether he had two different types of macroglobulins — one being an agglutinin and the other not Otherwise our total material of M component containing sera with increase in macroglobulins has been free from cold agglutinins It seems probable that this is a rare type of macroglobulin but that it advertises itself early because of the severe anemia The difference in the occurrence of cold agglutinins between this group and the control group is not statistically significant (table I)

It is interesting to note that cold agglutinins in our country probably are found as a serological reaction in atypical pneumonia and also, much more rarely, in some other infections It is well known that acute hemolytic anemia may occur after atypical pneumonia, and we have seen one such instance ourselves Probably the increased cold agglutinin titer is the explanation as the anemia disappears when the cold agglutinin titer falls

Tropical trypanosomiasis also gives high titers of cold agglutinins The chemical nature of these macroglobulins remains to be further investigated but it is evident that this reactive increase in macroglobulin is of the polyclonal type We do not know whether some of these purely symptomatic increases may be of the same high degree as in essential progressive macroglobulinemia It is known, however, that there is a marked decrease after successful treatment of the disease (3)

The *Paul Bunnel and ox cell hemolysin* tests were negative

It was already mentioned that only one patient — with obscure anemia and leukopenia — had a positive *antistreptolysin titer* (AST) (1/425), probably specific since it later decreased to borderline *Antistaphylolysin titer* (ASTA) was somewhat high (4 4) in one patient with the benign type of macroglobulinemia AST and ASTA were both less frequently elevated in these sera than in the control group sera (table I)

The fact that the *rheumatoid factors* have been shown to be macroglobulins makes this whole group of rheuma tests seem especially interesting In our series we

have performed the coated sheep-cell Waaler-Rose and acryl fixation test as well as F II A reaction The last two tests have been in use only in the latter part of the examination period The results were as follows

The classical Waaler-Rose test is of course the best known as it has been used for many years It has been performed on 30 sera available It was positive in 3 One patient had a rheumatoid arthritis and it is probable that he has a true rheumatoid factor The acryl fixation test and the F II A reaction were also positive The two other sera came from patients who had no signs of rheumatic disease One was a man born in 1914, who had symptoms of macroglobulinemia with moderate anemia, splenomegaly and a typical sternal puncture He was in quite good condition The other patient s history has been presented at some length by Waldenström (14) She has not had any malady that could be connected with her macroglobulin When we first saw her the macroglobulin content of her serum was quite high and she had marked cryoglobulinemia During the years her macroglobulin has decreased spontaneously and it has now almost disappeared This is one of the few instances of spontaneous decrease of an M component that we know of This type of macroglobulin as seen in patient G M (10, p 33) is obviously completely different from the so-called Waldenstrom's macroglobulin It is probable that the other serum also containing a high titer of rheumatoid factor (Waaler Rose 1/2048) belongs to a similar group, although this patient had clinical symptoms and has not been followed very long yet Both sera had a markedly elevated acryl fixation test and F II A reaction Although positivity of these three tests was more frequently seen among macroglobulin sera than among sera from the control group, the difference was significant only for the F II A reaction (table I)

Myeloma

Myeloma is of course our biggest group with M components Here we usually have very large increases in globulin of monoclonal type, and very commonly also a background" hypo-γ with or sometimes without M component Cases of the latter type have not been included, since pure hypogammaglobulinemia was outside the scope of this investigation

The results are as follows Eighty seven myeloma patients were investigated but in some patients only certain tests were performed The fact that the syphilitic serology was investigated even before the program with extensive serology was started gives us 94 myeloma sera from patients we have diagnosed ourselves, where the occurrence of *anti complementary* activity (Ac) in the serum could be judged One patient had a pyroglobulin and could therefore not be tested, but he should definitely be regarded as having an anticomplementary γ globulin Three patients showed Ac in dilutions of 1/30—1/40 this is regarded as low but definitely pathological Three had dilutions of 1/240—1/480 i e medium Four had extremely high dilutions (1/1920, 1/7680, 1/15720, 1/121680) It is perhaps worth noting that the last serum also was extremely high in antistreptolysin One of the medium-

level sera also had an antithyroglobulin titer of 1/25 These 10 positive sera thus give a percentage of about 10

The fact that 17 γ_A- and 29 γ_M containing sera were never found to be Ac might suggest that these molecules do not carry this property Altogether 17 (myeloma) + 29 (macroglobulinemia) + 8 (ess benign) = 54 sera with such components have been tested There is the proportion 0/54 with an anticomplementary effect as compared to 15/132 γ_G which is a significant difference ($P < 0,05$)

It is clear that Ac is not the same as an increase in one special antibody but we think it constitutes a molecular marker This completely unspecific physico chemical property of the γ globulin molecule has earlier been confused with the presence of non specific syphilitic reagins that were previously said to be common in myeloma

We have investigated 94 consecutive sera for *Wassermann etz*, without finding any indication of non specific reagins One patient had only a Meinicke reaction grade 3 where we do not know anything about old syphilitic infection Another man had all four reactions strongly positive and knew that he had a syphilitic infection It might seem as if this constitutes a low incidence of true syphilitic reagins but the disease is now so uncommon in Sweden that 1/94 must be quite characteristic for an elderly population

All 72 sera tested were negative as regards *gonococcal reagins*

Regarding *bacterial antibodies* 73 sera were tested with the Widal method there was never a titer above 1/40

The types of reactions detected by the *cold agglutinin* test (85), *Paul Bunnell* test (81) or *ox cell hemolysin* test (51) were all normal

Antistreptolysin was determined on 87 sera Four were positive, all having γ_G M components, 8 were borderline including $2\gamma_A$ The most interesting finding by far seems to be in patient A O

A O is a man born in 1886 He suffers from a classical myeloma with 7 S γ_G globulin of 7 g/100 ml Treatment with Melphalan has had an excellent effect on his general status and on his globulins His globulin value has decreased to 2,5—3 g% His anticomplementary titer 1/121 680 and his antistreptolysin 1/512 000 (not related to β lipoproteins) did not however, decrease with his gammaglobulins

It is evident that he has an enormous increase of a globulin that functions as an anti treptolysin It seems likely that the high antistreptolysin content is specific' in the sense that it is not related to lipoproteins but nonspecific in that such high titers never occur in immunisation experiments Antistreptolysin titers of pathological degree are otherwise rare (1/360 1/600, 1/850) The first of these patients had a strongly anticomplementary globulin the next may well have had a streptococcal infection The last however did not show any signs of streptococcal disease She had some of the rheumatoid tests positive too On the whole 4/87 seems to be a low percentage ($P < 0\ 05$) of positivity for the second most commonly positive of all tests that we have tried (table II)

Antistaphylolysin was determined on 72 myeloma sera It was positive only in

one (7 5) Clinically no explanation for this pathological titer could be found The Waaler-Rose reaction was positive (1/256) and the serum also contained C-reactive protein (4) It is possible that there was some staphylococcal process going on The frequency of positive ASTA was significantly higher (P < < 0 01) in the control group (table II)

The *rheumatoid factors* have been tested on the following numbers of different sera Waaler-Rose 79, acryl fixation test 49, F II A reaction 49 As already mentioned, the patient with high antistaphylolysin had also a high Waaler-Rose 1/256 without signs of joint disease This was the highest titer found There are three sera containing 1/64 None of the four patients mentioned had signs of joint disease Two patients had negative Waaler-Rose tests and had positive acryl fixation test (1/40, 1/80) for no obvious reason Two patients had strongly positive F II A precipitation test but the other tests were negative All patients discussed in this group had γ_G myeloma except the one with Waaler-Rose 1/64 who had γ_A increase

Essential, benign, monoclonal hyperglobulinemia (fig 2)

Let us now compare the results in the group having essential, benign, mono clonal hypergammaglobulinemia (γ_M excluded) with the myeloma findings

In the benign group *anticomplementary* activity was determined in 63 cases The increase in activity was quite low grade in 4 sera (1/7, 1/15, 1/10) These were not counted as positive One patient had a titer of 1/30 He showed a rich serology (AST 600, ASTA 3,7) and had a liver cirrhosis Another also had liver cirrhosis and a prostatic carcinoma (AST, ASTA positive) His Ac was 1/2 560 and 1/480 Liver cirrhosis may be a common cause of an increase in anticomplementary gammaglobulin (see fig 1) One man had no complicating disease His titer was 1/120 He died later from dissecting aortic aneurysm and hemopericard No explanation for his γ disturbance could be found at the post mortem in spite of the fact that myeloma was especially looked for

One patient (M F—Ac 1/480) has long been regarded as possibly suffering from myeloma She has pernicious anemia and this problem has been treated by S O Larsson in a recent publication (9) We have followed her γ globulin values, and her general status since 1956 has been quite unchanged (nearly 6 years) We are therefore inclined to regard her as a benign essential hyper γ

The most intriguing case is S Å, woman born in 1897 No signs of serious disease She has slight symptoms of myalgia Her case history will be given by Hällen in a forthcoming publication Her titers of anticomplementary activity have been 1/20 480

It is evident that Ac was not especially common among our patients in this group (5/63) and not, as it was in the myeloma group, statistically higher than in the control group

Syphilitic serology is difficult to discuss The man with the strongest Ac had a Meinicke reaction grade 2 Otherwise syphilitic reactions are negative in the benign group All 53 sera tested were negative as regards gonococcal reagins

In 64 sera *Widal reactions* were performed All were negative

The *cold agglutinin, Paul—Bunnel* and *ox cell hemolysin tests* were always negative (63, 63 and 59 sera)

Antistreptolysin titer was determined on 62 sera Two patients had a polyclonal increase as well, and had signs of liver cirrhosis Their high titers were in all probability caused by an increase in β lipoprotein (7) There are not many patients with positive results left Two patients with γ_G had unexplained titers of 1/300 or 1/360 one had a high CRP Two patients had increase in γ_A One had a sarcoma of the leg (see A R Waldenstrom 1964 16) The first had a titer of 1/500 the second 1/500

The most fascinating findings are the AST titers of 1/16 000 in patient A N and 1/8 000 in E N In neither of these two women was there any history of streptococcal infection and the high AST could not be related to an increase in β lipoproteins The clinical data will be discussed in another paper There was no significant difference in the frequency of AST between this group and the control group (table III) As in the control group *antistaphylolysin* (but not AST) was found positive in significantly (P 0 01) higher incidence than in the myeloma group

Rheuma factors were positive in 5 cases Two had active rheumatoid arthritis one had metastatic prostatic carcinoma and *sarcoidosis* the other 2 had no disease that could account for the serological findings

Auto-antibodies

It is hard to decide if *Coomb s test* indicates presence of a real auto antibody This reaction is commonly found in lymphatic leukemia but has otherwise not been specially looked for in this group It is not too uncommon in different conditions with polyclonal hyper-γ, and even in severe hypo γ

The only type of *auto-antibody* that is not really difficult to demonstrate is directed *against thyroglobulin* Skanse and Nilsson (12) have investigated this problem, but they used a large number of sera from patients with M components that came from patients in different parts of our country It was therefore difficult to get the clinical data necessary for a final judgement regarding the specificity

Thyroid antibodies were determined only in 14 sera, some of these not belonging to the present collection Only in one patient (K N with a marcoglobulin content of 1 0 g/100 ml) was the titer of antithyroglobulin pathologically increased (1/250) The *complement* fixation test was negative

One patient s history deserves special comments She has a slowly progressive myeloma with a γ_G increase too At this stage she had a titer of 1/2 500 She has later been on treatment with Melphalan with very strong reduction of her M component Her thyroid antibody titer has likewise decreased

Only one of the patients had a complement fixation of some magnitude (1/40)

In the benign monoclonal group there are also some patients with positive tests of the 34 tested 3 had 1/25, 2 had 1/250 and the third 1/250 000 without having any symptoms of clinical thyroid disease This patient died The post mortem disclosed no signs of myeloma For some reason that is hard to find,

almost all organs — except the thyroid[1] — were examined microscopically It is therefore impossible to tell if there was a round cell infiltration in the gland and also to state the degree — if any — of damage to the parenchyma

Conclusions and summary

One of the present authors (J W) has divided the conditions with an increased serum γ-globulin into the following groups (the chief results for serology contained in the present paper have been added)

1) *Monoclonal* (M component)
   γ_G ↑ (often anticomplementary)
   Essential benign (sometimes very high antistreptolysin or antithyroid titers)
   ↓ Myeloma (sometimes high AST)
   γ_A ↑ (never anticomplementary)
   Essential benign
   ↓ (no serological reactions found)
   Myeloma
   γ_M (macro) ↑ (never anticomplementary)
   Symptomatic (lymphatic leukemia) (WR,cold agglutinin)
   Essential benign (cold agglutinins)
   ↓ Malignant (cold agglutinins)
2) *Polyclonal*
   Symptomatic (auto immune disease, liver cirrhosis etc) (rich serology)
   Essential (rare)

The present paper deals with a number of serological reagins in conditions with monoclonal hyperglobulinemia of different kinds γ_G, γ_A, γ_M It was found that the titer of most of the factors examined was lower in some of these groups with monoclonal hyperglobulinemia than in a normal population, and much lower than in groups of cases with polyclonal hypergammaglobulinemia (liver cirrhosis, systemic lupus) This is probably explained by an inhibition in the formation of antibody molecules other than the M component itself with the monoclonal γ globulin increase, and accords well with the background hypogammaglobulinemia seen in most of these conditions It was noted that gammaglobulin with an anti complementary effect was quite common among the sera containing γ_G M components, but never occurred when γ_A or macroglobulins were increased This probably means that the groups interfering with complement function are present only on the γ_G molecules In three patients with big γ_G M component high titers of antistreptolysin could be found It has been shown that this anti streptolysin effect is not caused by the β-lipoprotein in these patients Among the sera with macroglobulinemia we found several with an increase in cold agglutinin titers This was never found in other sera (γ_G, γ_A) Also the rheuma factors were present in high titers in some of the macroglobulinemia sera One of these patients belongs to a special group with a tendency of the gammaglobulins to aggregate In this patient the content of highmolecular globulin decreased very markedly during an observation time of 4—5 years Auto-antibodies against thyroid substances were present in slightly increased amounts in some patients without clinical evidence of thyroid disease One such serum from a benign essential hyper globulinemia contained unusually high titers (γ_G) In one patient with γ_G

myeloma the antithyroglobulin titer was 1/2 500 One patient with macroglobulinemia had a titer of 1/250 without evidence of thyroid disease Our conclusion is that through the proliferation of one clone of plasma cells the daughter cells maintain their formation of gammaglobulin molecules with the original immunological pattern Occasionally this may result in an enormous amount of one specific antibody in a myeloma patient's serum without the existence of a corresponding inducing antigen In polyclonal hyperglobulinemia the general tendency to form a large number of antibodies is increased

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Chromaffin Granules in Certain Arteries

By

H Nordenstam and P O Wester

The occurrence of chromaffin granules localized in characteristic cells in human skin was first observed in 1956 by Adams Ray and Nordenstam (1) Chromaffin granules have subsequently been found in most human tissues and organs and in the tissues of various animals (2, 10 11, 12) Burn and Rand (4), Falck et al (8) Burn et al (5) also found chromaffin granules some being of a different type while Coupland and Heath (6 7) deny the occurrence of such cells In one of the above mentioned papers by Nordenstam and Adams-Ray an intimate and regular connection between vessels of various sizes and chromaffin granules was observed These observations prompted the present study in which the aim has been to record the occurrence of chromaffin granules in some arteries viz the carotid coronary internal mammary celiac middle cerebral dorsalis pedis arteries and the aorta These arteries were chosen mainly to cover various arterial dimensions The coronary and middle cerebral arteries were chosen because of their well known disposition to tonic contraction The study has not been restricted to the chromaffin granules only, attention has also been paid to the intensity of atherosclerosis

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Material

Specimens about 0 5—1 cm of arteries macroscopically fairly free from atherosclerotic lesions were collected from 10 autopsied cases in the following way

1 The carotid artery internal carotid artery 1—2 cm above the bifurcation
2 The aorta the top of the arch
3 The coronary artery the descending ramus of the left coronary artery 1 cm distal to the bifurcation
4 The internal mammary artery approximately at the same level as the cardiac valves
5 The celiac artery about 2 cm from the aorta
6 The middle cerebral artery immediately distal to the internal carotid artery
7 The dorsalis pedis artery in the middle of the dorsum pedis

The corpses were left in their beds for 3 hours post mortem and were then transferred

TABLE I Clinical data

Age (yrs)	Sex	Cause of death	Clinical remarks	Time between death and fixation (hrs)
8	♀	Skull fracture	Previously healthy	60
20	♂	Tumor of the brain	Previously healthy	9
22	♀	Generalized arteritis	Hypertension	44
32	♂	Carcinoma of the stomach	Previously healthy	30
48	♂	Tumor of the brain	Previously healthy	20
51	♂	Subacute encephaliti	Previously healthy	9
53	♂	Cirrhosis of the liver	Myocardial infarction	36
61	o	Cerebral hemorrhage	Rheumatoid arthritis	10
66	♀	Cancer of the stomach	Myocardial infarction	9
73	♀	Myocardial infarction	Previously healthy	12

to the hospital morgue, where the temperature was kept at + 4° C

Some clinical characteristics are recorded in table I

Methods

Fixation

From each part of the above mentioned arteries one portion was treated with 10 % neutral formalin, another with alcoholic formalin and a third with Orth s *solution*, after which the portions were embedded in paraffin and sectioned in the usual way The slides were mounted in balsam

Staining methods

The granules of the artery walls were assessed for chromaffin character according to the conditions stipulated by Lison (1953) and Gomori (1952) The following histological stains and histochemical reactions were used

1 Chromaffin reaction, i e formation of brown staining compounds by bichromate fixation
2 Argentaffin reaction Staining according to Masson using Fontana s solution
3 Azo-coupling reaction in alkaline solution Gomori s method with 2 amino-5 azo-toluol was used
4 Indophenol reaction The method with 2,6-dibromoquinonechloroimide according to Gomori was used
5 Ferric ferricyanide reduction test Method according to Lillie (1954)
6 Autofluorescence in ultraviolet light Unstained slides were examined in a Leitz Ortholux microscope with a UV lamp (3660 Å)

The following staining methods were also used van Gieson, Htx eosin and the Sevki modification of the Giemsa method

Results

In the UV-light microscope autofluorescent cells were localized and their staining properties then tested with other indices of chromaffinity If these tests were positive the cells were regarded as chromaffin cells Thus the number of cells containing chromaffin granules was measured in several sections of the specimens From the aorta a portion

measuring 1 cm was examined The number of chromaffin cells/section is given in table II In the same specimens the degree of atherosclerotic lesion was recorded independently by another investigator as follows

+ Traces of intimal and subintimal fibrous hyperplasia as in the common type of atherosclerosis

++ Moderate intimal and subintimal fibrous hyperplasia *as in the common type of atherosclerosis*

+++ Heavy intimal and subintimal fibrous hyperplasia as in the common type of atherosclerosis

++++ Atheromatous ulceration and/or calcification



Fig 1 Auto-fluorescent chromaffin cell close to the elastic lamina in a cerebri media The photograph was first made on Anscochrome daylight film in UV light (3 660 Å) and the transparency copied on to Kodak th ortho plate The specimen used had been fixed in alcoholic formalin and was unstained 1 200 ×

The sex distribution permits no conclusions

It has been shown earlier that the staining results for biopsies are superior to those with autopsy material In the latter there is no possibility of proving any regular connection between on the one hand the time elapsing between death and the collecting of the material and on the other hand the presence of chromaffin cells The chromaffin cells have not earlier been enumerated Adams Ray and Nordenstam, however, have made a comparison of the occurrence of chromaffin cells in abdominal skin and in skin from the calf Chromaffin cells were proved to be 4 times as numerous in skin from the calf as in skin from the epigastrium Analogously Adams Ray and von Euler have found that skin from the calf contains about 7 times as much adrenalin as skin from the abdomen These results may suggest that the number of chro-

Discussion

The material presented has been taken chiefly from older persons

A comparison between the youngest cases and the oldest ones reveals a much greater number of chromaffin cells in the latter group This may suggest that there is a positive connection between atherosclerosis and the presence of chromaffin cells in vessels Such a connection however is contradicted by another observation viz the result of the assessment of the atherosclerotic lesions The artery with the highest degree of atherosclerotic lesions (a dorsalis pedis) was free from chromaffin cells Nor does there seem to exist a clearly converse relationship as indicated by the observations on the aortas and the coronary arteries

TABLE II The figures indicate the number of chromaffin cells per section

Age (yrs)	Sex	Arteria carotis	Aorta	Arteria coronaria sin	Arteria mam int	Arteria celiaca	Arteria cer med	Arteria dors. ped
8	♀	0/6 −	0/5 −	0/7 −	0/9 −	0/7 −	2 −	0/13 −
20	♂	0/7 −	3 −	0/8 −	0/6 −	0/4 −	0/8 −	0/7 −
22	♀	0/5 ++	0/6 ++	0/10 ++	0/9 +	0/5 +++	0/9 +	0/8 +
32	♂	0/4 +	0/4 +	5 +	1/6 −	1/4 +	lost +	0/4 ++
48	♂	0/7 ++	2/5 ++	1/8 +++	0/8 ++	3 ++	10 ++	0/8 ++++
51	♂	3/4 ++	0/4 ++	3/5 +	0/7 −	1/5 ++	13 +	0/4 +++
53	♂	1 ++	46 +++	35 +++	3/7 ++	3/5 +++	12 +++	0/8 +++
61	♂	1 +++	35 ++	54 +++	4/5 −	39 +++	52 ++	0/5 ++++
66	♀	0/4 ++	5 +++	2 ++++	4 +	2/7 ++	91 +	0/7 +++
73	♀	2/5 +++	1/4 ++	7 ++++	0/11 +	3/7 ++++	13 ++++	0/8 ++++

+ to ++++ indicate the degree of atherosclerosis

maffin cells in vessels increases in the same degree as does the hydrostatic pressure If so, one should find the largest number of such cells in the dorsalis pedis artery and the smallest number in the middle cerebral artery The vessels examined were chosen partly on account of this theory The result, however, affords no confirmation of this assumption The only suggestion possible is that the number of chromaffin cells seems to decrease in the peripheral direction

In previous papers the role of the chromaffin cells as possible transmitters of the automatic regulation has been considered An unusually large number of chromaffin cells should then be found in vessels which have a well known disposition for spasm Therefore the coronary artery and the middle cerebral artery were selected Both of these vessels had an abundance of chromaffin cells A vessel comparable to the coronary artery as regards thickness and hydrostatic conditions is the

internal mammary artery, which altogether had very few chromaffin cells These observations may perhaps support the above mentioned theory

Experimental investigations have proved that the staining-properties of the chromaffin cells are influenced by inflammatory processes of different kinds From this point of view one of the cases presented is of particular interest A young woman had a hypertension which was discovered by chance and was probably due to a stenosis of the renal artery This stenosis was operated on, but post operative complications arose and the patient died The microscopic investigation revealed a generalized arteritis non specific in type It was found in arteries of different sizes and had caused several stenoses This case was the only one where no chromaffin cells could be found The absence of chromaffin cells in this case agrees with previous observations on tissue affected by inflammation (3)

This study was intended as a screening of possible relationships between chromaffin cells and atherosclerosis The material is small and therefore gives only scattered information It is premature to try to draw firm conclusions from the results obtained but they indicate that a further analysis of a larger series of specimens might give interesting information

Summary

The number of chromaffin cells in certain arterial walls from 10 autopsies has been determined No definite correlation between the degree of atherosclerosis and the number of chromaffin cells was found Vessels with a spastic disposition, such as the coronary artery and the middle cerebral artery, show a large number of chromaffin cells Previous experimental observations concerning the influence of inflammatory processes on the chromaffin cells seem to be confirmed

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Fever and Elevated Erythrocyte Sedimentation Rate[1]

A Cross Study through a Medical Department

By

I E Bottiger and L Molin

Patients with fever and elevated erythrocyte sedimentation rate are common in all medical departments, and are in fact encountered in any hospital department Diagnosis usually calls for a great deal of investigation — if indeed it is arrived at The literature records a large number of studies on fever of unknown etiology (5, 23 24 27 29) and a smaller number on series of patients with elevated erythrocyte sedimentation rate of obscure origin (1a, 19, 21) However it has been said that surveys of this type are seldom of any practical help when faced with the individual patient (25) The causes of disease change and the scenery of disease shifts from time to time so that it becomes necessary at regular intervals to analyse the situation and discover which are the cases predominating among those exhibiting fever and an elevated erythrocyte sedimentation rate of obscure origin In an attempt therefore to discover what might underlie the elevations of fever and ESR observed, we carried out a cross study on all the patients hospitalized at the department of Medicine on three occasions during the course of one year

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Material and methods

On Jan 24 March 1 and Oct 11 1961 every patient in the Department of Medicine with a morning temperature on two consecutive days of 37 0 C or more and all those with an ESR of 30 mm or more in one hour were recorded On these occasions 97 98 and 95 % respectively of the 134 beds in the department were occupied

The diagnoses were ascertained by questioning the physician in charge and by later reading of the case records In cases in which there was some doubt as to the cause of the fever or elevated ESR data were collected from later hospitalization of the patients, if any

[1] This paper is number IX in a series of studies of fever of unknown origin

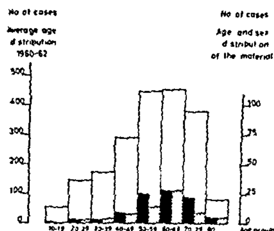


Fig 1 Age and sex distribution of 167 patients (71 men (☐) and 96 women (■)

Results

A preliminary survey of the three groups of patients revealed no differences in their composition as regards sex, age, or diagnosis, the series was therefore subsequently treated as a single unit

Altogether *167 cases* fulfilling the requirements were noted on the three occasions *Fever alone was present in 30 patients (18 %), elevation of the ESR was noted in 137 patients (82 %)* Eighty (60 %) of the latter group also had fever, but this was in most instances slight, and only eight ESR patients had a body temperature in excess of 38 0 C

The age and sex distribution will be found in fig 1 The diagnoses are given in table I The patients included in the series for fever alone are given there in the first column (ESR 0 to 29 mm/1 hour) The ESR patients who were at the same time febrile or subfebrile are not indicated in any particular manner as the elevation in fever and ESR was in every instance correlated and in accordance with the diagnosis made

The diagnosis was arrived at during hospitalization in 152 cases (91 %), on later hospitalization in 9 instances (6 %), and still remains obscure after a long interval in 5 cases (3 %) It should be noted that the investigation was not designed to discover when the diagnoses were made, but only to ascertain what they were

Discussion

The age distribution of the series agrees fully with that in the medical department and shows no special features (fig 1) The sex distribution in the series as a whole showed a predominance of women (96 women as against 71 men) However, the whole of this preponderance of women was accounted for by the group of patients with fever but without ESR elevation, which comprised 25 women and 5 men In the ESR patients, then, the sex distribution was equal (71 women and 66 men)

As regards the *fever cases*, it should be noted that there is at this medical department some bias in the selection of patients due to the situation of the hospital and to some extent to the investigational and teaching duties Further, in the Stockholm area, a large number of acute cases of fever are referred to special hospital units for infectious diseases

The limit of 37 0° C was selected, not because it has any real justification, but because it has come to be regarded by both laymen and practitioners as the boundary between fever and "no fever" (cf 5)

TABLE I

Diagnosis	Patients included because of					
	Fever	ESR				
	ESR 0—29	30—69	70—99	100	Total	
Cardiovascular system						
Myocardial infarction	2	9	3	—	14	
Thrombo-embolic disease (other)	3	3	1	—	7	
Cardiosclerosis	3	6	—	—	9	
Endocarditis	—	1	—	—	1	31
Respiratory tract						
Bronchitis pneumonia	6	14	3	—	23	
Pleurisy	—	2	—	—	2	
Sinusitis	—	1	1	—	2	27
Alimentary tract						
Ulcers and melena	3	4	—	—	7	
Gastritis enteritis colitis	1	—	—	—	1	
Diseases of gall bladder and bile ducts	—	1	1	2	4	
Cirrhosis of the liver	—	11	—	—	11	23
Urinary tract						
Acute infections	1	5	4	—	10	
Chronic infections	1	9	4	1	15	
Nephrotic syndromes	—	—	1	2	3	28
Collagen disease	—	6	4	3		13
Malignant disease						
Localized	—	8	4	1	13	
Hematological	1	3	—	4	8	21
Diverse diseases	8	10	1	—		19
Unknown etiology	1	3	1	—		5
Total	30	96	28	13		167
			137			
Percentage of total no of ESR pat		70	20	10		

[1] Includes such conditions as barbiturate intoxications unspecified anemia varicose ulcers subcutaneous h matoma etc

The causes of fever are given in table I consisting of nonspecific infections of the lungs and respiratory tract (6 cases) of the urinary tract (2 cases) and of the intestine (1 case) of fever associated with thrombo embolic disease and cardiac incompetence with pulmonary stasis (8 cases), and fever during current melena (3 cases) The group diverse cases included two women with pronounced premenstrual elevation of body temperature four

cases of active thyrotoxicosis, one of chronic myeloid leukemia, one of herpes zoster, and one of barbiturate intoxication

The *fever cases* call for some comments Most series of patients with fever of unknown origin contain a predominance of women (5, 7, 8) One reason is that women without any true fever are included in the studies — many women of fertile age have a rise in temperature of up to 38 0° C during the premenstrual period, often without being aware of it

Further, temperature regulation seems to be more unstable in women than in men Ziolko (32) studied basal body temperature in neurotic women and found appreciable deviations from the normal curve One group was characterized, among other things, by 'fever" Ziolko expressed the view that mental influences produced this altered basic temperature Böttiger (7) has also pointed out that in a series of fever patients there was a group of women who, in addition to body temperature elevation, showed several neurotic traits in the absence of any signs of organic disease In malignant diseases, too, women react more frequently with fever than men This is exemplified in studies of renal carcinoma (8), which show that 33 per cent of the women, but only 17 per cent of the men, with renal carcinoma exhibited a rise in body temperature which subsided following operation The mechanism underlying this temperature elevation in malignancy is not known (see further below) There are, in fact, still wide gaps in our understanding of the regulation of body temperature Variations in temperature associated with the menstrual cycle suggest that hormonal influences play some part in its regulation This is also borne out by the high fever noted in thyrotoxicosis The extent to which the adrenal hormones affect normal body temperature is not known There are on record studies reporting temperature rises in young persons in stress situations (28) The underlying causes are not understood, but the liberation of adrenaline has been considered So called "neurotic fever" might also be regulated via the adrenal catecholamines

In fact, it has quite recently been demonstrated that adrenaline or noradrenaline injected into the cerebral ventricles of an unanesthetized cat *lower* a raised body temperature, while injection of 5 hydroxytryptamine raises the temperature The experiments suggest that normal body temperature is maintained by a delicate balance in the release of adrenaline, noradrenaline and 5 hydroxytryptamine in the hypothalamus (15)

It is not known to what extent the fever inducing steroid etiocholanolone participates in normal temperature regulation

The fever group includes one case of chronic myeloid leukemia In cases of leukemia, and in other malignant diseases, there is discussion as to whether the cause of fever is infection or whether the basic disease itself is responsible — as was generally believed earlier In renal carcinoma, for instance, there is convincing evidence that the fever observed is *not* of infectious etiology (8) In leukemia on the other hand, many

TABLE II Importance of ESR values at different levels (mm/1 hour)

0–(1)	Not normal	Polycythemia (or coagulated sample)
(1)–29	Probably normal	May reflect serious disease possibly malignant and even with metastases
30–69	Never normal	Need not necessarily reflect serious disease even when of long duration Most common infections and diseases are accompanied by a raised ESR in this group
> 70	Never normal	Is found in a small number of diseases usually of malignant character as a rule accompanied by pronounced serum protein changes (collagen diseases some malignant diseases myeloma macroglobulinemia) Renal disease Benign hypergammaglobulinaemia (Waldenstrom)

authors now seem to regard most of the febrile episodes as of infectious nature In acute leukemia Raab et al (26) found infection to be demonstrable during 102 of 149 febrile episodes in 55 patients Other investigators (3 30) had earlier reported just over 50 per cent of febrile episodes to be of non infectious nature, but their recent experience (Frei personal communication 1962) seems to suggest that in two thirds of cases or perhaps almost always fever in leukemia is of infectious nature However Frei drew attention to the fact that the incidence and cause of fever may vary in different forms of leukemia In cases of non infectious fever antibiotic therapy usually has no effect on the temperature elevation and may easily lead to secondary infection with resistant bacteria (4)

The diagnoses in the ESR cases are given in table I The first point to be noted is that the bulk of the patients had an ESR of between 30 and 69 mm in one hour (70 %, of the ESR cases are found in this range) This is the level to which the ESR rises in most common diseases and infections The number of cases and diseases decreases as the ESR increases above 70 mm hour especially when the level exceeds 100 mm/hour (17 % of the ESR patients had values between 70 and 99 mm, 8 % over 100 mm/hour) In the presence of these high ESR values, it is chiefly systemic diseases of the type of collagenosis malignant conditions and renal disorders which have to be considered — three disease groups which together accounted for 66 % of the cases in which the ESR exceeded 70 mm/hour

The distribution of the ESR values in the present series prompted a classification of cases which may be of value in clinical practice (table II) A limit of 30 mm in one hour was selected as a practical boundary since both statistical and practical reasons suggest that any values above that level are abnormal Under the 30 mm level, as illustrated in table II values may either be normal or reflect disease

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garded as a normal ESR Westergren's original limits are now regarded by many investigators as too narrow, However, Westergren's values may certainly without reservation be taken to apply in young persons The difficulty arises when dealing with persons of more advanced age Is there normally a rise in ESR with advancing age? Eckerström (13) studied healthy elderly persons and came to the conclusion that *no elevation of the ESR takes place* Later statistical analysis of his material (12) did, however, show that in fact some elevation occurred This was also observed by Wilhelm and Tillisch (31) The difficulty in cases of this type is to decide upon what should be regarded as "normal" in association with advancing age Should some arteriosclerosis with its sequelae, and a certain degree of arthrosis with secondary changes in surrounding tissues be assumed to be part of the normal' aging process? *Both these disease groups have been* maintained to lead to some elevation of the ESR There is no doubt that persons of very advanced age may have an ESR of less than 10 to 15 mm in one hour Are these healthy persons supernormal? Other factors which may perhaps be included in the normal aging process are changes in the serum protein pattern with a fall in albumin content Further studies of healthy elderly persons are called for to clarify these problems

As regards the ESR values, in particular, it is important to note that the cases were included in the series *because* of their elevated values Accordingly, the present study is in no way capable of elucidating the incidence of different ESR values in any given disease Another important point to be borne in mind, especially against the background of the statement made of malignancy as a cause of particularly high ESR values (table II), is that malignant disease, even with metastases may be present in the absence of any noteworthy rise in ESR This is clearly exemplified by the conditions in renal carcinoma Despite several statements to the contrary (18, 22) the belief has been maintained — especially in Sweden — that a hypernephroma or renal carcinoma is always associated with a very high ESR In cases of excessive ESR it is correct to consider carcinoma of the kidney and to take every possible measure to detect the presence of malignancy in that organ But several studies (8, 9, 18, 22) have shown that many patients with renal carcinoma have no such rise in ESR In Böttiger's series (9), 46 % of the patients had a *normal or only slighly elevated* ESR (30 mm/hour or less), while only 22 % had particularly high values (over 70 mm/hour)

The diagnoses, as given in table I, call for little comment In a large proportion of the cases the cause of the ESR level was current disease of the circulatory system (infarction, venous thrombosis, etc) possibly with an infectious element and infections of the respiratory or urinary tract The high *incidence of cirrhosis* of the liver should be noted A high ESR is a fairly early sign in liver cirrhosis and is connected with a diffuse increase in the gamma globulin fraction in the serum Elevation of the ESR may be observed without

other signs of liver incompetence, and the correct diagnosis may not be arrived at until liver biopsy is performed

Special attention should be given to the collagen disease, malignant disease, and tuberculosis groups As regards the fact of these three conditions, there was initially no suspicion of *tuberculosis* in the present series But follow up examinations revealed the presence of tubercle bacilli in a patient with chronic infection of the urinary tract, further, in one patient with liver cirrhosis who came to autopsy there was, in addition to the cirrhosis also fresh areactive tuberculosis — probably provoked by the corticosteroid therapy Tuberculosis *is regularly found in series of fever of unknown origin and in those of obscure ESR elevation* And this still applies in the nineteen sixties Five tuberculosis cases of fatal outcome which remained undetected clinically, all presenting as febrile conditions, were published in another connexion (10) In the United States (20) and elsewhere it has been pointed out that the watch for tuberculosis should not be *diminished The* danger that the indiscriminate use of steroids may provoke tuberculous infection should also be emphasised (*cf* 14) Cortisone administration was probably the cause of the *tuberculosis in the case* of liver cirrhosis mentioned above as also *in two of* the other cases of fatal outcome similar observations have been *recorded* in several *quarters*

Malignant diseases are usually diagnosed without too long a *delay* Lilje strand Olhagen (19) *pointed* out in 1955 that a high ESR *remaining* unaccounted for after clinical *investigation* is only occasionally a sign of undetected malignancy According to the same authors, the danger of missing malignant disease is greater in patients with a low ESR — as has been already mentioned

Nevertheless, despite a strong suspicion of malignant disease, a considerable period elapsed before the diagnosis was verified in two cases in the present series

Case 1 Female 67 years, became fatigued, lost weight had a subfebrile temperature, and was found to have anemia (hemoglobin 8 5 g/100 ml), the ESR was very high (135 mm/hour) and the electrophoretic alpha globulin fraction was greatly elevated Clinical investigation disclosed no cause of the symptoms A gynecological tumour was suspected after 6 months surveillance Explorative laparotomy revealed glands in the abdomen a biopsy specimen proved too shallow for confident diagnosis She was treated for a tentative diagnosis of Hodgkin s disease which was not verified until autopsy was performed *13 months after the initial examination*

Case 2 Female 56 years with diffuse pain in the left flank for three or four months An ESR of 48 mm/hour was the only positive finding A second examination six months later disclosed that a parenchymal opacity had developed in the left lung and tomography revealed a large pleural lesion Radiation therapy had no effect and she succumbed 18 months after the onset of the symptoms Autopsy disclosed massive infiltration by a poorly differentiated tumour containing plentiful connective tissue the primary focus of which could not be identified

Finally the collagenosis group presents great diagnostic difficulty This is not only because the familiar diseases lupus erythematosus disseminatus periarteritis nodosa, etc are difficult to

diagnose with certainty (discussed by Böttiger in 6), but perhaps chiefly because two syndromes have emerged in latter years which are still not clearly delimited either from each other or from other disease — and perhaps least of all from malignant diseases These syndromes or symptom complexes are the anarthritic rheumatoid syndrome (2) and giant-cell arteritis (1, 17)

The features of these two 'diseases" are largely the same Older persons develop constitutional symptoms consisting of fatigue, weight loss, marked anemia, usually a very high ESR and $alpha_2$-globulin elevation They also complain of stiffness and muscular pain These features are common to both 'diseases"

Case 3 Male, 60 years with 12 months' history of transient joint and muscular pains admitted for ESR investigation He had an ESR of 104 mm/hour, slight anemia (hemoglobin 10 8 g/100 ml), was subfebrile and electrophoresis showed a pronounced alpha globulin rise Investigation at first gave negative results two months later thickening of the temporal arteries was noted Biopsy showed giant cell arteritis and steroid therapy had a prompt effect on the constitutional symptoms, the ESR etc

The two conditions differ in that giant cell arteritis, of which temporal arteritis is a special form, is diagnosed by positive biopsy findings and that it is a disease carrying a serious prognosis, lesions chiefly eye damage sometimes leading to blindness, may occur if the disease is not treated in time

Case 4 Female, 68 years, with stiffness and pain in the back and thigh muscles, fever (38 to 39° C in the evening), was admitted for nvestigation Her body temperature was around 38° C, she had anemia (hemoglobin 9 5 *g/100 ml*), an *elevated* ESR (117/hour), and a marked electrophoretic rise in alpha globulin Biopsy of specimens taken from the temporal artery and the liver showed the vessels to be normal, no signs of arteritis Initially treated with steroids which had a favourable effect on the muscular symptoms and the ESR Now almost two years *after treatment*, she still complains of some muscular weakness and fatigue, but is otherwise in good condition.

Anarthritic rheumatoid *disease, on* the other hand, is of benign character Biopsy of vascular and other specimens gives negative results, without any signs of arteritis, and a positive reaction to rheumatoid factor is elicited in about half the cases — although usually *in* low *titre These* and other *findings* prompted Bagratuni to regard his" disease as a special form of rheumatoid arthritis He emphatically refused to accept the idea that anarthritic rheumatoid disease is a form of arteritis These problems will be considered in another connexion

There is without any doubt a great deal of uncertainty in the literature at present as regards the delimitation of these syndromes, and they are in fact confused in all their variants *Gower* (16) drew attention to the current *confusion* and advised that in obscure cases the term fever of unknown origin should be retained, the designation collagenous disease not being used unless there is positive evidence of such a condition However, *Gower* admitted that in these cases of fever of unknown

etiology which show features described above as belonging to anarthritic rheumatoid disease or giant cell arteritis there are features closely resembling the collagen diseases The difficulty, or even impossibility, of differentiating between these syndromes and those accompanying malignant disease should also be noted All the symptoms mentioned may also occur in areactive tuberculosis and in tumour diseases — not only constitutional symptoms such as weight loss, fatigue anemia, elevated ESR, and a rise in $alpha_2$ globulin, but also muscular pain and joint symptoms The features of anarthritic rheumatoid disease are frequently characteristic but in many instances a complete roentgen investigation is required in order as far as possible to rule out the presence of malignant disease as precipitating factor

It may be of interest in this connexion to consider also the syndrome known as Wissler s disease (11) hitherto described only in children and young persons It is a syndrome characterized by protracted, irregular fever with leucocytosis a high ESR and anemia and sometimes also transient signs of cardiac involvement joint pains etc Accordingly the syndrome in many respects resembles the symptom complexes described above The view has been expressed (11) that Wissler s disease should be regarded as due to an abnormal connective tissue reaction possibly provoked by staphylococci and that it has certain transitional forms approaching rheumatoid arthritis Perhaps the Wissler syndrome is an infantile or juvenile equivalent of anarthritic rheumatoid disease?

Summary

In order to observe possible shifts in the causation of fever and elevation of the erythrocyte sedimentation rate at a medical department, a cross study was carried out on three occasions during the course of one year

No noteworthy changes in the causes of fever and erythrocyte sedimentation rate elevation have been observed during the past decade The occurrence of fever and elevated erythrocyte sedimentation rate is discussed with particular regard to the collagenous tuberculous and malignant disease groups

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The Proactivator (Plasminogen?) Determination in Plasma During Fibrinolytic Therapy

By

Sverre Blix

A method for the quantitative determination of proactivator in human plasma has previously been published (1) It was stated that if proactivator is a part of the human plasminogen molecule the results in this report will also reflect the plasminogen content otherwise expressed plasminogen was determined as proactivator So far, it has still not been proved that human plasminogen and proactivator are different substances

The test system consists of bovine plasma (which is the source of fibrinogen plasminogen and inhibitors) diluted human test plasma (proactivator or human plasminogen) streptokinase in *high concentration* and thrombin

The *great excess of* streptokinase in the system 80 000 or 160 000 U/ml *undiluted* human plasma) makes it also possible to determine *proactivator* (plasminogen?) content in plasma containing streptokinase or urokinase in concentrations used for *thrombolytic therapy* In testing non fibrinolytic plasma streptokinase can be added before or after the human test plasma but in testing fibrinolytic plasma the streptokinase should preferably be added prior to the test plasma

0 1 ml citrated bovine plasma,
0 05 ml streptokinase (8 000 U/ml)
0 05 ml citrated human test plasma (diluted 1/10 or 1/20 in buffer or saline)
0 1 ml thrombin (30 N I H U/ml)

If desired all volumes may be doubled For further details see the original publication The per cent of proactivator (plasminogen?) is read on a reference curve obtained from dilution series of normal human plasma (in fig 1 the 100 per cent value corresponds to undiluted plasma actually tested in dilution 1/10)

Fig 1 shows the results when three dilution series of the same normal plasma (undiluted 1/2 1/4 and 1/8) are tested in the system the first series containing no streptokinase (×) the second series 1 T I D ( ) and the third

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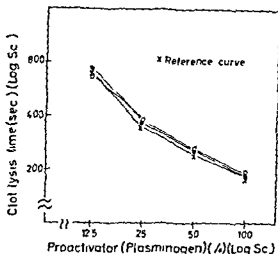


Fig 1 Dilution series of plasma with and without streptokinase tested in the system

series 4 T I D of streptokinase (●) (and all series further diluted 1/10 before testing) T I D refers to the 'titrated initial dose", which expresses the amount of streptokinase giving a lysis time of ten minutes in an undiluted plasma clot

Streptokinase in the test plasma did not influence the determinations The results were essentially identical when fibrinolytic plasma activated with urokinase was tested

There was no loss of proactivator activity when the dilution series had been stored for one hour at 4° C or room temperature As the plasminogen most likely is converted to plasmin during this period, the method probably measures the combined plasminogen/plasmin content in plasma

Summary

It has still not been proved that proactivator and human plasminogen are two different substances A previously reported method for the quantitative determination of proactivator will probably also give the plasminogen concentration in human plasma

The present report shows that the results are unaffected by addition of streptokinase or urokinase to plasma in concentrations used for thrombolytic therapy The method might be of value in plasminogen determinations on plasma from patients during such treatment

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Acute Viral Hepatitis in Norwegian Track-finders

An Epidemiological Study in Norway 1962—63

By

ODD D VELLAR

Track finding (orientating) usually takes the form of a race over a course of 3—14 km through woods and other types of terrain The competitors must check in at a varying number of control points and have to find their way with the aid of map and compass To make running easier the usual clothes have consisted of light shoes, short socks running shorts and a shirt with short sleeves some of the competitors have used legshields

The competitions which often attract several hundred participants are usually held from April to June and from August to November

Hepatitis in Swedish track finders

From Dec 1957 it became evident to health authorities in Sweden that hepatitis occurred with rapidly increasing frequency among track finders (7 From Dec 1957 to Oct 1963 568 cases were reported In the county of Jönköping with about 280 000 inhabitants and 900 active track finders the hepatitis morbidity in 1960 of the whole population and of the track finders was 16 and 2 400 per 100 000 respectively (4)

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The majority of the recorded cases of hepatitis among track finders were men The remarkably few cases found among females can not be accounted for by the predominance of men participating in the sport (25 000 to 3 000 respectively)

The onset of disease by month was clearly cyclic with a maximum in November February a minimum in April June with another peak during August followed by a second drop in September October This typical variation in the incidence of hepatitis in track finders was not found in the rest of the Swedish population During the maxima of incidence in Dec 1960 and 1961 more than 40 % of all the cases of hepatitis in Sweden occurred among track finders

Secondary cases in the normal *non track finding* environment were reported on only three occasions (7)

The collected epidemiological (3 4 6 7) and clinical (5) data have supported the view that most of the cases have been serum (inoculation) hepatitis

In 1962 the problem was considered so serious that all the competitions for the spring season this year were cancelled and special prophylactic measures had to be undertaken for the autumn season The hepatitis incidence among Swedish track finders dropped dramatically after this prophylaxis was introduced (7)

TABLE I Information on jaundice among track finders obtained from questionnaires

	Total no of returned questionnaires	No reporting jaundice before April 1962		No reporting jaundice during the year April 1962—May 1963
		Prior to engagement in track finding	After engagement in track finding	
Males	1,609	64	41	12
Females	249	5	4	1
Total	1,858	69	45	13

Investigations in Norway

As track finding is an extremely popular sport here it was considered interesting to evaluate the extent of the hepatitis-problem in Norway At the time this investigation was initiated in the spring of 1962 there was no record of a single case of hepatitis among Norwegian track finders In 1962 there were in all 6,000 men and about 4,500 women who were members of clubs affiliated to Norges Orienteringsforbund (The Norwegian Track-finders' Association), but not all of these were active participants

Material and methods

To establish contact with track finders who had had or who suffered from jaundice during the course of the investigation, a questionnaire was sent out in the spring of 1962 to Norwegian track finders via their regional and local clubs These clubs were also responsible for recording the number of track finders who had received the questionnaire This, however, was not successfully carried out

The questionnaire contained two questions concerning the occurrence of jaundice the track finders should report if they had had jaundice before April 1962 or contracted the disease in the period April 1962/May 1963

The present investigation extended from the beginning of the track finding season in April 1962 and was concluded in May 1963 so as to include all who could have been infected during the autumn season

Those track finders who answered the questions affirmatively were sent a supplementary questionnaire containing a number of questions concerning competitions in which they had participated during the last six months before the illness contacts with people suffering from jaundice, whether they had been blood donors, whether they had had blood samples taken the occurrence of cuts and scratches during track finding and the possible infection of others etc In addition doctors and hospitals that had treated such cases were asked to communicate their diagnosis and comments concerning the clinical picture in each individual case

All replies which were received before 31/12/1963 have been included in the material used The total number of replies received is shown in table I In addition to the cases contacted through the questionnaire, information was also received from 22 other jaundice cases, some of these were male track finders who reported directly without using the questionnaire others were through reports from doctors and hospitals and in some cases from track finders who knew of friends who were or had been ill These cases

TABLE II Reported cases of hepatitis among track finders military personnel and in the general population

Group	Years	Population	No of cases	Rate pr 100 000
Track finders	4/1962–5/1963	1 858	13	700
Males		1 609	12	746
Military personnel	1962	35 000	5	14
General population	1962	3 645 000	458	13

also received the supplementary form and the clinical picture was supplemented by the doctor who had treated them This information however is not included in the statistical assessment of the original material which consists only of cases who sent in the primary questionnaire

Results

It can be seen in table I that 12 men and 1 woman contracted jaundice in the period of investigation (April 1962/May 1963) The information obtained from the doctor or hospital that had treated these cases makes it probable that all these 13 cases were of viral hepatitis Table II shows the comparative attack rates for track finders (male and female) male track finders the Norwegian population as a *whole* and military personnel (2) It is seen that the attack rate for the group under investigation is about 50 times greater than that of the groups used as a basis of comparison

With respect to the monthly distribution of the onset of jaundice in the 13 cases all were found in the autumn and winter months with a maximum in December In 4 of the 13 cases there is a possibility of iatrogenic inoculation caused by blood samples or blood donorship in the last six months before the illness, in 8 cases this possibility does not exist and in one case information is lacking *on this point*

In none of the 13 cases is there evidence of contact with non track-finders suffering from jaundice In 2 cases it has been stated that they had visited other track finders while these were ill

In 4 cases there was less than 4 weeks and in 9 cases 8—19 weeks between the last track finding event and the onset of jaundice

All the track finders who had been ill stated that they had participated actively in several track finding *events* (3—21) in the last six months before the illness Only one of those in the group who were ill stated that in the last six months before illness, he had never received cuts and scratches in connection with track-finding another said that cuts and scratches were rare but the 11 others were of the opinion that it happened *occasionally* or *frequently*

No positive information is available on secondary cases that have occurred

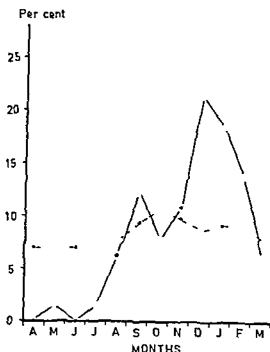


Fig 1 Relative monthly distribution of 65 cases of hepatitis among track finders and of 16 095 cases reported in the general population during the years 1953–1962
— Track finders
General population

among non track finders (in three cases the information available is insufficient)

In the above only the 13 cases that contracted hepatitis, April 1962/May 1963 and who communicated this on the questionnaire have been discussed However, information was received in 80 cases of icterus which had developed among track finders after they had begun this sport

Of the 80 cases (75 males and 5 females) 15 cases were excluded because the jaundice was proved to have no connection with track finding

The remaining 65 cases are assumed on the basis of the information received from hospital/doctor and/or track finders, to be hepatitis, and a connection between track finding and the disease is probable These cases are collected from the period 1953—1963 and fig 1 shows the relative monthly distribution of these cases compared with that of the general population during the years 1953 —1962 There is a considerable difference between the two distribution curves

Discussion

As can be seen from the figures in table II, *the frequency of hepatitis* in Norwegian track finders far exceeds that in military personnel and in the Norwegian population as a whole During the period of investigation (April 1962/May 1963) the attack rate was about 50 times that recorded in the two groups used for comparison (1962)

The epidemic curve indicated by the monthly distribution (onset of jaundice) (fig 1), is similar to that reported by the *Swedish investigators (7) This particular* epidemic curve is quite different from that for hepatitis in the general population which shows only small fluctuations from season to season

The mode of transmission of the infection is in most cases difficult to establish Among the 13 cases included in the current investigation there is nothing to suggest contact with established epidemics in the normal non track finding environment

In 4 of these cases however iatrogenic inoculation is possible since blood samples were taken during the 6 months prior to the disease

All the 13 track finders with jaundice had participated in competitions in the last six months before the onset of jaundice and most of them were aware

of ha ing received cuts and scratches during the race

No informat on is available on sec ondary cases among non track finders and th s lends support to the hypothesis that it is serum hepat t s that one is deal ng with

The assumpt on that most cases have been serum hepat t s and that the trans m ss on of the infect on has occurred during track find ng compet t ons is supported by the part cular ep demio log cal s tuat on of the races Two factors are probably respons ble for the spread of the infect on 1) group ng of people under cond t ons w th poor san tary fac l t es and 2) nearly all of the compet tors get scratches and wounds during the track f nd ng races (1)

If a carrier of the virus gets injured the blood can infect other compet tors w th s m lar cuts through contam nated a h ng water hand bas ns us ng the same towels s tt ng on the same benches espec ally n bath room or poss bly from thorn bushes or barbed w re wh ch ha e been nfected by a carr er by d rect contact or perhaps by fl es Both serum hepat tis and ep dem c hepat t s can be transm tted by inoculat on in th s way The lack of to let and vasl ng fac l t es dur ng the track find ng compet t ons fa ours the faecal oral spread of ep dem c hepat t s too

The p ophylax s As a consequence of the nc ea e of cases of hepat t s among rack f nders propl ylact c measures ha e been undertaken A compet t on dress co er ng the extrem t es as n t oduced Better l yg ene as recom men led n connect on w th wasl ng procedures and a period of personal quarantine for the d seased ind viduals came in force

Summary

This invest gation has documented the high incidence of hepatitis among Nor wegian track finders amounting to 50 t mes that found in military personnel and in the general populat on

Most of the ca es have probably been serum hepatitis judged from the pre sented ep demiological data and the transm ssion of the infection has in all l kel hood taken place by contaminated blood from injured carriers of the v rus be ng inoculated into other compet tors w th sim lar wounds by way of washing water hand bas ns towels etc

The prophylact c measures include better protect on aga nst wounds and scratches hyg en c preca t ons in con nection with wash ng procedures after the races and personal quarant ne for the diseased ind v duals

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G LLE G RINGERTZ O & ZETTERBERG B In p ess
6 NATv H T norske Lægefo en 83 127 1963
7 ZETTERBERG B & R GERTZ O In press

Der 14 Deutsche Kongress fur ärztliche Fortbildung wird in der Zeit vom 22 bis 27 Mai 1965 (Himmelfahrt) wieder in West Berlin stattfinden

Auskunft erteilt Kongressgesellschaft fur ärztliche Fortbildung e V, 1 Berlin 41, Klingsorstr 21

Le Xe Congres Europeen d'Hematologie se tiendra a Strasbourg (France) du 23 au 28 8 1965

Les principaux sujets traites seront

La structure des protéines sanguines et des hemoglobines
L'etiologie et la chimiotherapie des leucemies
Le premier temps de l'hemostase
L'hemophilie et sa therapeutique
Les problèmes genetiques en hematologie
L'hematologie geographique
La chimie de substances de groupe
Les enzymes erythrocytaires
Aspects morphologiques et fonctionnels des lymphocytes etc

Certaines seances seront consacrees a des problemes interessants plus particulierement la transfusion (separation des eléments figures du sang, conservation du sang et de la moelle osseuse a basse temperature, etc)

Tous renseignements complementaires seront fournis par le Docteur J Lewin, Centre de Transfusion Sanguine, 10 rue Spielmann, Strasbourg, (France)

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The Geriatric Unit De Gamles By Copenhagen, and The Hormone Department
State Serum Institute Copenhagen, Denmark

Adrenocortical Function and Serum Cholesterol in Elderly Persons Treated with Triparanol

By

BENT MACKEPRANG SVEND G JOHNSEN and TORBEN GEILL

During recent years human hypercholesterolaemia has been treated in two ways by diet or by drugs True, a replacement of dietary fat having a high content of saturated fatty acids (butter fat pork, drippings, etc) with foods having a high content of polyunsaturated fatty acids (maize oil soya bean oil) does lower the serum cholesterol (by 15—20 %) in most cases However the patients tend to keep less strictly to the diet after some time and the vegetable oils used so far are apt to cause appreciable dyspepsia Furthermore, the most recent studies have revealed that polyunsaturated fatty acids in large amount cause a vitamin E deficit so that this vitamin has to be administered at the same time A more serious claim is that the polyunsaturated fatty acids when administered in high doses may give rise to necroses in the brain heart and liver Accordingly cholesterol lowering drugs are of importance both as a therapeutic method *per se* and as a supplement to dietetic treatment

Drugs which lower the serum cholesterol have widely different targets Sitosterol reduces the absorption of cholesterol from the alimentary tract, choline promotes the transport of cholesterol to the peripheral fat depots, the unsaturated fatty acids increase the breakdown of cholesterol in the liver, and many agents inhibit cholesterol synthesis at some stage or other Among the most recent drugs mention may be made of Triparanol which inhibits cholesterol synthesis, but only at its last link from desmosterol to cholesterol However since according to some workers desmosterol too has a tendency to be deposited in the arterial wall the clinical effect of this preparation is in some doubt

From a scientific point of view, however Triparanol is of great interest Among other features, its influence upon the cholesterol content of the adrenal glands and upon adrenal function in general, has been a subject of discussion

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Eisalo and Talanti (1) have reported histochemical studies on the effect of Triparanol upon the rat adrenal cortex The rats were given the drug, parenterally or by mouth, in doses of 2—30 mg daily for periods ranging from 10 to 85 days The lipid in the fascicular and reticular zones disappeared entirely These changes were observed in all the treated rats and were most marked in the rats which had received the highest doses of Triparanol

The effect of Triparanol upon adrenocortical function in man has been investigated by Melby et al (5), who found that the administration of 1 g Triparanol daily for 10 days to healthy subjects reduced their basal adrenal secretion of cortisol and also impaired the adrenocortical response to pyrogen stress On the other hand, Marks et al (4) found no evidence to indicate that Triparanol, when used in the dosages ordinarily employed in clinical practice (0 25 to 1 0 g daily for 10 to 57 days) caused clinical manifestations of adrenocortical insufficiency, either during the basal state or during periods of stress such as a surgical operation, in a patient who has normal adrenal function at the start of therapy It must be mentioned however, that the latter authors found a moderate decrease in the basal urinary 17-hydroxycorticosteroid excretion but no significant change in free plasma 17-hydroxycorticosteroid levels

The present study was designed to ascertain whether long term treatment with Triparanol (supplied by ASTRA (as Mer-29) and GEA (as Tramin)) in the ordinary therapeutic dosage (250 mg daily) influences the basal adrenocortical function and the ability of the adrenal cortex to respond to the administration of corticotrophin

Material and methods

The investigation was carried out on 4 patients, all males selected according to the following criteria 1) No diabetes or other endocrine diseases, hepatic disorders, heart failure, or chronic renal disease involving renal failure 2) Full control of bladder function and ability to empty the bladder completely In all 4 cases rectal palpation had revealed a normal not hypertrophic prostate, and catheterization had shown the bladder to be empty immediately after voiding 3) The patients had to be mentally intact to the extent that they could collaborate in collecting their own urine, so that none was lost during the experimental period

Case 1 Aged 91, admitted 24 6 60 Diagnosis Cerebral arteriosclerosis

Intercurrent diseases during the experimental period

1) 17 2 62 Fever of unknown cause (39 1 C) for 2 days
2) 24 2 62 Pneumonia with fever up to 39 0° for 2 days treated with penicillin)

Case 2 Aged 71 admitted 9 12 61 Diagnoses Cerebral arteriosclerosis Right sided hemiparesis

Intercurrent diseases during the experimental period

1) 19 2 62 Pneumonia (temperature 39 5 C) Temperature returned to normal after penicillin for a few days
2) 9 8 62 Urinary infection (temperature 38 C) treated with furadantin for 10 days
3) 31 12 62 Pneumonia temperature 38 6 C which returned to normal after penicillin therapy for 3 days
4 7 1 63 Low grade fever because of urinary infections and minor pneumonias treated with sulphonamides and penicillin

Case 3 Aged 77 admitted 24 6 60 Diagnoses Seq of cerebral thrombosis Right sided hemiparesis Soon after admission the patient was able to fend for himself

Intercurrent diseases during the experimental period

1) 15 11 61 Bronchopneumonia with a temperature up to 38° C Soon improved on penicillin

Case 4 Aged 76 admitted 26 10 49 Diagnoses Cerebral arteriosclerosis Mild right sided hemiparesis

Intercurrent diseases during the experimental period

1) Since May 1962 treated with phenantoin because of seizures with generalized convulsions
2) 15 9 61 Penicillin therapy because of pneumonia
3) 24 2 15 5 and 26 5 1962 Elevation of temperature to 39 C for one day recovered spontaneously
4) 22 9 62 Urinary infection with vomiting and a septic type of fever Despite parenteral fluid therapy and penicillin in million unit doses, the general condition steadily deteriorated and the patient died on 4 11 62

Autopsy revealed a cyst like softening posteriorly in the left temporal lobe No signs of recent changes to explain the clinical picture However the post mortem report is regrettably deficient because of a technical error in recording the autopsy findings

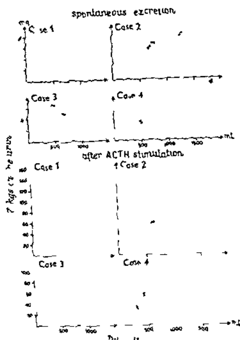


Fig 1 Ratio of hormone excretion to 24 hour urinary output The encircled value representing the spontaneous excretion in case 4 is presumably due to an error (cf text)

Laboratory studies

Prior to the treatment with Triparanol the following laboratory studies showed in all the patients values which were within the range of normal 1 Liver function tests (alkaline phosphatases in serum bromsulphalein retention test pyruvic acid transaminase and glutamic-oxaloacetic acid transaminase content in the serum icteric index thymol reaction and Takata Ara) 2 Electrolyte content in serum (potassium and sodium) 3 Serum cholesterol 4 Serum creatinine 5 Urine analysis for protein and sugar 6 Haemoglobin level in the blood and erythrocyte sedimentation rate Furthermore, body weight and blood pressure were checked and the cardiac status was assessed by electrocardiography and chest radiography

The urinary excretion of 17 ketogenic steroids (17 KGS) was determined by the so-called Norymberski II technique (2) in the modification described by Jorgensen (3) After each determination of spontaneous 17-KGS excretion a corticotrophin tolerance test was done This test was made long and intensive in order to obtain a measure of the maximum reserve capacity of the adrenal cortex Quick acting corticotrophin (Acton©) was administered i m 25 I U four times daily for 4 days and the 17 KGS excretion was determined on the 4th day

These hormone analyses were carried out at 4 7 week intervals 3 times before the administration of Triparanol 6 times during

TABLE I Urinary excretion of 17 KGS (mg/24 hours) in 4 patients before during and after treatment with Triparanol, 250 mg daily The determinations were carried out at 4—7 week intervals and comprise spontaneous excretion as well as the excretion following ACTH stimulation

	Case 1		Case 2		Case 3		Case 4	
	Spont	ACTH	Spont	ACTH	Spont	ACTH	Spont	ACTH
Before	8 0	153	7 1	68	6 0	37	4 6	32
	7 0	142	5 8	77	6 0	35	4 7	31
	6 6	111	6 4	57	5 2	22	3 5	61
During	7 6	76	6 4	69	6 0	28	3 6	[1] —
	7 1	49	7 7	38	5 0	33	[1] —	40
	7 9	73	5 3	52	5 2	38	3 1	57
	7 1	44	8 2	65	3 8	58	4 5	39
	8 5	73	6 1	29	5 1	53	3 8	33
	[1] —	56	7 1	37	4 7	49	[3] 10 1	48
After	7 8	76	5 5	56	6 6	85	5 2	101
	6 8	61	5 9	63	6 3	49	[2] —	—
	7 1	92	5 8	59	4 8	70	—	—

[1] Collection of urine failed
[2] Patient died
[3] Presumably erroneous determination (cf text and fig 1)

the treatment, and 3 times after the treatment had been discontinued However, as case 4 died before the experimental period was over, only one hormone analysis was obtained after the discontinuation of the medication

Throughout the experimental period blood samples were drawn to determine the serum levels of potassium, sodium, and cholesterol on the day prior to the corticotrophin tolerance test At the same time, blood pressure and body weight were checked

After the treatment with Triparanol the liver function tests and the serum creatinine determination were repeated

Treatment

All the patients were treated with Triparanol 250 mg daily for about 6 months (from 24 3 to 29 9 1962)

Results and conclusion

The calculated hormone values pre suppose a correct collection of the 24-hour urines Since the collection of urine entails a certain inaccuracy, probably in particular in aged patients, we have plotted the 17-KGS values against the corresponding daily urinary output in fig 1 One value (the spontaneous out put in case 4) is outside the range of the other values, and the daily output is so abnormally high that this value was ex cluded For the other values there was no relationship between the daily output of urine and the 17-KGS values, and this is taken to indicate that the collec tion was reliable

Table I lists the 17 KGS values found (spontaneous values as well as values following corticotrophin tolerance tests) in the 4 patients before, during, and after the experimental period.

Table II sets out the corresponding cholesterol concentrations in the serum.

The course of the experiment in each individual subject is illustrated in fig. 2.

In case 1 the spontaneous 17 KGS excretion remained constant throughout the entire period. The corticotrophin stimulation values fell somewhat during the treatment period. However, the lowest value was 5 times higher than the spontaneous excretion. After the treatment the values were about identical with those in the treatment period.

In case 2 the spontaneous 17 KGS excretion remained unchanged. The stimulation values varied a good deal, during the treatment period they were perhaps a bit lower than before and after.

Case 3 showed a very dubious tendency to somewhat lower spontaneous 17 KGS values during the treatment period. On the other hand the stimulation values were completely unaffected by the treatment, there being a trend of gradual increase throughout the treatment.

Case 4 showed no changes before and during the treatment. The increase at the end of the after period is presumably due to the intercurrent fever. It is interesting to note this patient's enormous adrenal reserve capacity.

On the whole we found negligible changes in the hormone values. It is of interest to note that in all 4 subjects the adrenal reserve capacity was constantly very high, the production of steroids increasing about 8 fold during the corticotrophin stimulation.

TABLE II Serum cholesterol (mg/100 ml serum) in 4 patients before, during and after treatment with Triparanol 250 mg daily. Determinations carried out at 4—7 week intervals

	Case			
	1	2	3	4
Before	191	183	243	281
	226	204	246	272
	191	200	249	262
	205	—	—	—
During	190	177	183	202
	165	166	168	216
	176	168	185	217
	144	156	172	235
	150	176	148	204
	125	209	185	175
After	212	250	269	254
	247	212	258	—
	200	154	267	—

As might be expected from these findings there was no change in serum electrolytes or blood pressure during the treatment, furthermore body weight and the result of liver function tests remained unchanged.

Serum cholesterol values fell by 20—40 mg/100 ml during the treatment period. As a rule the fall occurred quite soon, whereupon the values remained fairly constant throughout the period. There was no definite tendency to an increase during the long treatment period. After Triparanol was withdrawn, the serum cholesterol level rapidly in-

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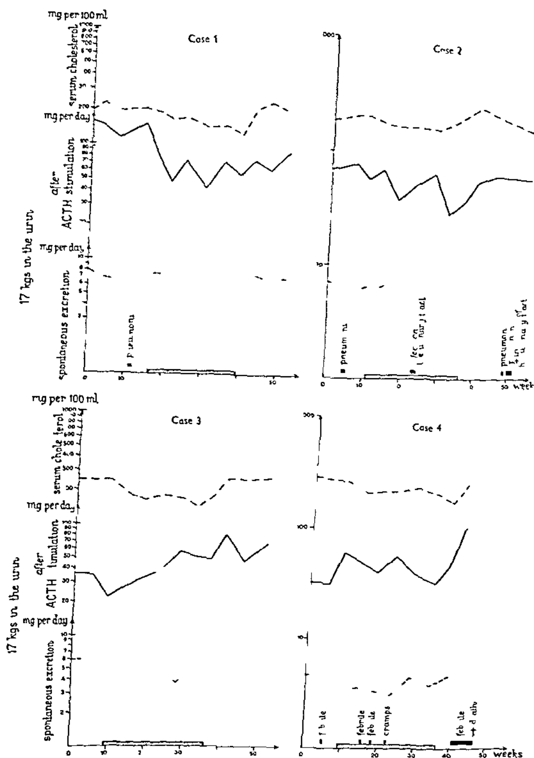


Fig 2 Serum cholesterol and adrenocortical hormone excretion in the urine in patients treated with triparanol Diagram drawn on semilogarithmic paper

Treatment with triparanol (250 mg per day)
—— Serum cholesterol
—— 17 KGS in the urine after ACTH stimulation
- - Spontaneous excretion of 17 KGS in the urine

creased to the initial values, in some cases perhaps to a slightly higher value

It is concluded from the present study that Triparanol administered in a dosage of 250 g daily for 6 months to old persons, does not reduce the reserve capacity of the adrenals, so that in this respect the treatment does not entail a risk

Summary

Four men, aged 71–91 years, were treated for 6 months with Triparanol in doses of 250 mg daily

Adrenocortical function remained unaffected by the treatment, the urinary excretion of 17 ketogenic steroids following ACTH stimulation being 5—10 times higher than the spontaneous excretion throughout the experimental period During the treatment, the patients serum cholesterol decreased by 20—40 % of the initial values After the treatment was discontinued, the serum cholesterol rose to a little above the initial values

There were no changes in body weight, blood pressure, serum potassium, serum sodium or liver function during the treatment

Acknowledgement

This investigation was supported by a grant from the F L Smidth Jubilee Foundation

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Hypokalemia and Hypertension

A Presentation of Four Cases Including a Case of Primary Aldosteronism

By

JENS CHRISTIANSEN, LEIF HAGERUP and BENT NIELSEN

During recent years the differentiation between primary and secondary aldosteronism in hypertensive patients has become a matter of great clinical and therapeutical interest

One of the prominent features in the picture of aldosteronism is a lowered concentration of potassium in the plasma In order to delineate the frequency of hypokalemia in hypertensive states a retrospective study of a consecutive series of patients admitted to the medical wards of this hospital during the years of 1960 –1962 was performed A diagnosis of arterial hypertension was established in a total of 238 patients This group comprises cases admitted because of hypertensive disease as well as cases with hypertension as an accidental finding The plasma potassium concentration was measured in 152 of these patients and in 46 cases values below the lower normal limit (3 6 mEq/l) were found on one or more occasions

Twenty eight of the 46 patients escaped the evaluation as they had received treatment with chlorothiazide or related drugs prior to the measurement In only one of these patients was there a suspicion of primary aldosteronism As this case is noteworthy from other points of view also a detailed report will be presented below (case 4)

Out of the remaining 18 cases a severe renal insufficiency was demonstrated in four patients, a condition not infrequently complicated by renal potassium loss and hypokalemia

In 9 patients the renal concentrating capacity was normal (a spontaneous specific gravity above 1 022) and a diagnosis of a primary aldosteronism therefore seems unlikely The hypokalemia was mild amounting to a few tenths of a mEq only

One patient died and the autopsy revealed no suprarenal abnormalities Finally one patient showed one sub

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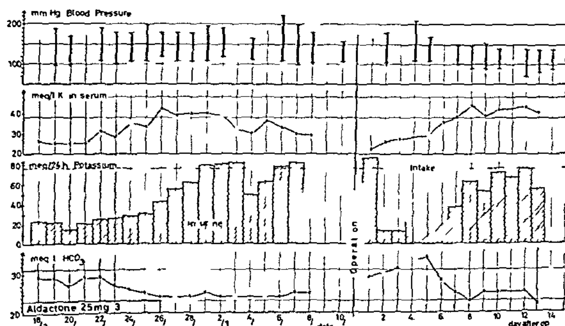


Fig 1 Main features of potassium metabolism B P and standard bicarbonate of case 1 during the treatment with potassium and Aldactone® and following the operation On the first two post-operative days cortisol and cortisone were administered

normal value amidst a long series of measurements within the normal range, probably an analytical error

The remaining three cases will be presented here with a brief comment on the diagnostic procedures and the treatment

Case reports

Case 1 A woman of 64 was first admitted to the department June 1961 with the sole complaint of vague abdominal distress One year earlier she had suffered a cerebral attack of thrombosis and a transient hemiparesis For several years a moderate hypertension had been present On admission the B P was 190/120 mm Hg The physical examination and X ray of the digestive canal revealed nothing abnormal Serum creatinine concentration and an intraveneous pyelography were normal but persistent isostenuria was found Leucocytes were present in the urine in a number of 1—8 per high power field and an erythrocyte was occasionally seen Otherwise the urine was normal In spite of a normal bowel function and the absence of vomiting the blood chemistry showed a permanent hypokalemia (2 0—2 3 mEq/l) alkalosis and intermittent elevation of the plasma sodium concentration No clinical signs of hyperadrenalism were found and muscular weakness was not demonstrated

The twenty four hour excretion of 17 ketosteroids was 6 2 mg (normal range for the patient s age 3—11 mg/24 hours) and a determination of the 17 ketosteroid excretion by a chromatographic separation technique showed a total of 3 94 mg with normal values for the different fractions The twenty four hour excretion of 17 ketogenic steroids was on two occasions 9 6 and 10 9 mg respectively i e at the upper normal limit (10 5 mg/24 hours)

The fasting blood glucose was normal (77—106 mg/100 ml) as was the eosinophil count (63 per μl) and the plasma magnesium concentration (1 89 mEq/l)

A diagnosis of primary aldosteronism was suspected and the 24 hour urinary excretion

of aldosterone was determ ned Values of 17 and 18 µg were found on two subsequent da s (normal range 2—19 µg/24 hours)

As the pat ent was non-cooperat ve though not psychot c and urgently wanted to leave the hosp tal further invest gat ons had to be abandoned for the t me being

Af er an attempt at su cide the pat ent was readm tted four months later The blood electrolyte values were essent ally unaltered and n Feb 1962 she was transferred to the Med cal Department for extens on of the previous invest gations The B P was st ll elevated but lab le ranging between 140 80 and 220/110 mm Hg The adm nistrat on of potass um chloride could not ra se the plasma potass um concentrat on However the s multaneous adm n strat on of a potass um salt and sp ronolactone (Aldactone®) brought the plasma potass um level with n the normal range (f g 1) A renal aortogram was normal A retroperi oneal oxygen insufflat on was planned but could not be accompl shed because of the pat ents anxiety

Because of the pers stent hypokalem a not abolished by the oral adm n strat on of potass um salt and a pos t e sp ronolactone test t was dec ded to explore the suprarenal glands surgically This intervention was further ad ocated by the constant sostenuria and the vary ng though moderate hyper tens on

The right s de was first explored An isola ed cort cal adenoma of the s ze of 2 × 3 cm was found f g 2 It was enucleated leaving he rest of the gland Thereafter it was decided not to explore the left s de The immed ate pos -operat ve course was uneventful

M croscop call the mass remo ed was of a glo nerular structure here and there with a fasc culate arrangement Hyperem a and great amo nts of l p ds were demonstrated S gns of mal gnanc were not fo nd (K Schourup M D)

An analys s of the t mor for the content of o costero ds showed he follow ng values o sol 14 0 cort sone 0 6 and aldos erone 0 5 µg 2 35 g of t ssue DOC could not be detected



F g 2 *From the operation on case 1* The arrow po nts to the adenoma n ts place before enuclea t on

Dur ng the f rst week follow ng the opera t on the blood electrolyte values slowly approached the normal levels and repeated control determinations have ever s nce been normal The B P decreased during the f rst ten days post-operatively and was after 2 weeks normal 135—140/70—80 mm Hg Controls n the out pat ent department have later shown the B P to be sl ghtly elevated and fa rly constant 150—160/90—100 mm Hg Isostenur a has pers sted

One year after the operat on the twenty four urinary excret on of aldosterone was found to be at the lower normal lim t (2 0 and 1 8 µg 24 hours)

On ambulant psychiatric exam nat on the pat ent has been found unstable but episodes of psychot c character have not been present *The social anamnes s has disclosed severe env ronmental partly matrimon al problems in the l fe of the pat ent*

Case 2 A man of 52 was adm tted to another hosp tal after a traffic accident He presented superf cial wounds of the frontal region amnes a and cl n cal s gns of a cerebral concuss on A lumbar puncture showed a water-clear cerebrosp nal flu d wi h 1044 erythrocytes per ml The B P was 280 150 mm Hg on admiss on and the pulse rate was

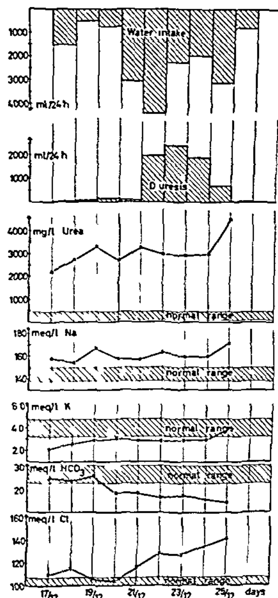


Fig 3 A diagram of the water and electrolyte metabolism in case 2

80 per min Because of the brain lesion the fluid intake was restricted during the following days The first four days the B P was between 190 and 250 mm Hg systolic but fell suddenly on the sixth day The patient became unconscious with clinical signs of shock and during the next seven hours he was anuric

The patient was transferred to the neurosurgical department of this hospital Signs of intracranial hemorrhage or focal cerebral damage could not be found, and four hours after the transfer the patient was brought to the renal insufficiency unit for further treatment

During the following two days the oliguria persisted (20—180 ml/24 hours) and the B P slowly increased to the former level 200—230/100—125 mm Hg Tracheotomy and mechanical respiration were necessary because of insufficient respiration The patient became increasingly uremic with a blood urea of 330 mg/100 ml, and hemodialysis was started two days after arrival The plasma electrolyte values, however were not compatible with a diagnosis of acute renal failure as the main factor in the clinical picture potassium 2 8 mEq/l sodium 167 mEq/l chloride 105 mEq/l and standard bicarbonate 25 mEq/l

During three successive attempts at hemodialysis the patient every time developed a clinical picture of shock after 10—15 min duration of the extracorporal circulation Simultaneously the plasma sodium concentration decreased and in spite of repeated improvement in the patient's condition following infusion of hypertonic saline, further treatment with the artificial kidney had to be given up

A diagnosis of primary aldosteronism was considered but the normal plasma chloride concentration and the lack of alkalosis did not seem to support this view As the patient was still unconscious an oral test with spironolactone was considered impracticable and preparations for parenteral use were not available

The respiration now spontaneous, was superficial and with a high frequency Furthermore the patient was clinically judged to be slightly dehydrated and it was therefore decided to administer isotonic glucose solutions and sodium chloride The condition gradually improved during the following four days The diuresis increased to a maximum of 2440 ml/24 hours Nevertheless the plasma electrolyte values remained unchanged and besides hyperchloremia and hypernatremia an acidosis of an increasing degree was now found The patient was

TABLE I Plasma electrolyte values of case 3

Admitt no	Potassium (mEq/l)	Sodium (mEq/l)	Chloride (mEq/l)	Stand bicarbonate (mEq/l)	B P (mm Hg)
I	3 1	140	99	25	200/110
II	3 4	140	101	26	170/100
III	3 3	133	106	22	230/140

slightly more awake, but experienced several convulsive seizures presumably evoked from the temporal region An EEG was highly abnormal with activity of low frequency in the right temporal region

Finally the temperature rose to 40 C the X ray of the chest showed infiltrations of both lung bases and the patient succumbed on the ninth day in the hospital after twenty four hours of oliguria and shock not influenced by vigorous treatment

Autopsy (Institute of Forensic Medicine, University of Copenhagen) The brain was edematous with necrosis of the central grey matter especially of the anterior basal ganglia on the right side

The kidney showed no ischemic injuries but arteriolosclerosis arterial muscular hyperplasia interstitial fibrosis and numerous fibrous glomeruli

The heart showed a moderate enlargement with hypertrophy of the left ventricular wall

The lungs were hyperemic without greater pneumonic infiltrations

The left suprarenal gland presented a tumor of the size of 1 5 × 1 5 cm with a greyish brown color Microscopically it was composed of large foam-cell like elements mixed with areas of small cells with scanty amounts of intensely colored cytoplasm The cells were arranged in solid masses without signs of malignancy From a histo-pathological point of view it was concluded that the tumor might have been aldosterone producing Analysis for corticoid content was not performed

Fig 3 shows the electrolyte values

Case 3 A woman of 56 with an untreated hypertension of six years duration was first admitted to the department in 1959 because of hypertensive encephalopathia She was treated with pempidini bitartras (Perolysene©), and the B P initially 200/130 mm Hg decreased to 160/100 mm Hg ECG showed a left heart strain and the X ray of the chest showed an enlargement of the left side of the heart A grade II hypertonic fundus was seen at ophthalmoscopy The serum creatinine concentration and the urinary concentrating capacity were both normal

The patient did well during the treatment but she could not attend regular controls and four months later the out patient department s control and the treatment were abandoned

$1^1/_2$ years later she was readmitted with cardiac insufficiency, mental impairment and episodes of confusion The B P was 230/120 mm Hg the eye backgrounds showed a hypertonic fundus grade II–III and the EEG was severely abnormal with a focus in the right temporo-frontal region A right carotis angiogram revealed nothing but arteriosclerosis A moderate diabetes was present

After two months she experienced a right sided hemiparesis The B P was 240 130 mm Hg Guanethedini sulfas (Ismelin®) 10 mg a day and hydroflumethiazidum(Rontyl®) were administered The reduction of the B P was moderate and more potent drugs or larger doses were avoided in order not to cause a critical reduction of the cerebral circulation The patient was very confused and she was ten days later transferred to the psychiatric department

After another ten days she was admitted to the department for the last time because of

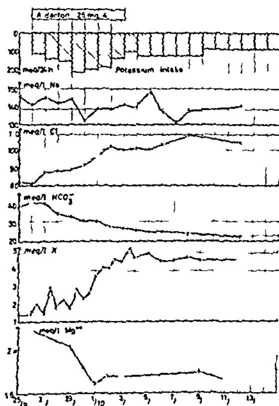


Fig 4 Case 4 Main features of the electrolyte metabolism during the treatment with potassium and Aldactone®

pareses of the right sided extremities and confusion The B P was 240 150 mm Hg and the patient s state was changing between stupor and agitation She died two days later

The *autopsy* (K Schourup M D) showed an emollition of the left hemisphere and pronounced left cardiac hypertrophy The kidneys showed slight arteriosclerosis The left suprarenal gland was transformed by a cortical adenoma measuring 4 5 3 × 4 cm Microscopically the adenoma was composed of a partly trabecular partly alveolar arrangement of cortical cells without signs of malignancy In the right gland a structure of the same character was seen but it was not macroscopically visible The cells contained moderate amounts of lipid but no hyperemia was seen

The plasma electrolyte values obtained on the three admittances are shown in table I

Case 4 A 69 year-old retired postman with diabetes mellitus well controlled with 20 I U of insulinum isophanum (Insulin Retard®) daily Because of a mild hypertension, he had periodically for some years received treatment with drugs of the chlorothiazide group Because of pulmonary stasis he was treated in an other hospital with hydroflumethiazide (Rontyl®), and he felt well on discharge walking away from the hospital

In the course of the next few days he developed muscular weakness and mental confusion and was after four days admitted to the psychiatric department No psychiatric disturbances were found The laboratory examination revealed urine (+) acetone (+) protein, + glucose, blood urea 27 mg/100 ml alkaline phosphatases 10 7 K A units, GOT 6 9 units GPT 3 7 units (normally below 1 7 and 1 5 units respectively), Hb 17 1 g/100 ml ECG showed a bigeminal rhythm He was adynamic with slight pretibial edemas In spite of the heart rhythm digitalis was added to the treatment with diuretics and the following day the patient was transferred to the medical department

Measurements of the plasma electrolytes here showed potassium 1 4 mEq/l sodium 145 mEq/l chloride 80 mEq/l and standard bicarbonate 39 mEq/l The ECG was unchanged

Immediately after the physical examination the patient suddenly became unconscious He was pulseless and no heart action could be detected Half a minute later resuscitation was started with external chest massage and mouth to-nose respiration Subsequently intubation with positive pressure ventulation was established and an infusion of a glucose solution containing 51 mEq of potassium per liter was started Five minutes later spontaneous heart action was recorded and after 45 minutes the respiration was adequate

The administration of potassium was continued parenterally as well as perorally and two days later treatment with spironolactone (Aldactone®) 25 mg four times a day was started As seen from fig 4 the electrolytes of the plasma became normal in the course of 8 days and remained so after withdrawal of spironolactone Insulin treatment

was stopped and has not since been required An intravenous pyelogram was normal and no signs of hyperfunction of the suprarenal glands were manifest

A follow up examination after 3 months showed a healthy man leading a normal life without cardiac complaints The blood elec trolyte values were normal, B P 200/105 *mm Hg and the eyes showed a hypertonic* fundus of grade II

Discussion

It would appear from the group of patients referred to in the introduction to the present paper that the concomi tance of hypokalemia and hypertension is a relative frequent observation in an ordinary medical practice This agrees with the demonstration by Hilden and Krogsgard (9) and by Wrong (21) of the coincidence of severe hypertension and hypokalemia as well as with the de monstration by Laragh et al (13) of an increased aldosterone secretion rate in patients with malignant hypertension

The hypokalemia in hypertensive states is certainly always a result of an increased mineralocorticoid effect (al dosterone) The diagnostic problem is to settle whether the hypertension and the hypokalemia are the *secondary* symp tomes of a primary suprarenal di order tumor or hyperplasia) or whether the hypokalemia may have been caused by an angiospastic disease or by some treatment that the patient has under gone It must be emphazised tha the latter secondary hypokalemia in itself may be a life threatening complication

In primary aldosteronism a rise of the plasma potassium concentration has been obtained by the administration of potassium salts (6) But Conn (3, 4) and other investigators (5, 15) all under line the difficulty in this syndrome of bringing the plasma potassium level back to normal merely by potassium loading

On the contrary a potassium defi ciency because of the use of diuretic drugs will be cured by a potassium load

The renal potassium excretion in hyperaldosteronism can be reduced by the simultaneous administration of potas sium chloride and spironolactone The result is an increase of the plasma po tassium concentration (11, 19) In nor mal persons or in patients with benign essential hypertension without hypokal emia the treatment seems to have no in fluence upon the plasma potassium level

The effect of the combined administra tion of spironolactone and potassium chloride in a case of primary aldoster onism appears from our case 1 (fig 1) while case 4 is an example of a potas sium depletion that is reversed by potassium loading, the aldosterone an tagonist apparently being unnecessary (*fig* 4)

Spironolactone is nevertheless of little value in the differentiation between primary and secondary hyperaldoster onism as the drug will act as an antago nist in both clinical states

However a diagnostic hint may be found in the values for the blood pressure and the plasma potassium Usually the hypokalemia is pronounced and the hypertension of a moderate degree in primary aldosteronism while a severe hypertension and a moderate decrease of the plasma potassium level are the typical features in hypertensive patients

with a secondary hyperproduction of aldosterone (4, 8, 9)

The measurement of the 24-hour urinary excretion of aldosterone may be informative, especially if a reduction in the value is demonstrable post-operatively, as was the case with our patient (case 1)

The exact figures give no information concerning the nature of the suprarenal hyperfunction Small increments may be found in patients with an adrenal *tumor while high values may be met* with in cases of secondary hyperaldosteronism (10)

The diagnosis may finally be settled by the measurement of the corticoid content of the tumor removed The values for the cortisol and aldosterone contents of the tumor found in our case 1 were definitely higher than the figures for normal adrenal cortical tissue obtained by Neher (16) A definitive diagnosis was unfortunately not established in the other two patients as a corticoid analysis of the tumors was not performed

A routine measurement of the plasma volume might have been of value As pointed out by Biglieri (2) the hematocrit value *is decreased in many* cases and the plasma volume always increased

In case 2 cerebral contusion, anuria, hypernatremia, hyperchloremia, hypo kalemia and hypertension were present The patient was dehydrated As pre*viously* pointed out by Luetscher and Blackman (14) and later summarized by Anthonisen et al (1) this syndrome may be seen in patients with cerebral damage Steinmetz and Kiley (20) described cases of anuria following lesions of the "visceral" brain and the limbic system and suggested a renal vasoconstriction as *the trigger mechanism In our* case it was impressive to note, firstly that the administration of water was beneficial, indicating that the dehydration was important (consistent with the views presented in a Lancet editorial (12)) and secondly that the patient gradually be came more acidotic This is usually not the case in hyperaldosteronism even with renal insufficiency (13)

Anthonisen et al (1) suggested hemodialysis as a possible treatment of such patients In our patient treatment with the artificial kidney was unsuccessful, probably because of a sodium loss to the outer fluid of the kidney If hemodialysis *is indicated we therefore suggest* that the sodium concentration of the dialyzing fluid should be equal to or slightly above the plasma sodium concentration

Even in retrospect it seems impossible to decide whether the trauma of the head with localized encephalomalacies, the unconsciousness with fluid loss and an abolished thirst regulation, the hyper tension and nephrosclerosis, presumably pre existent, or activity of the suprarenal *cortical adenoma was the main* factor of the complex clinical picture

In case 3, presenting a *malignant* hypertension with a moderate reduction of the plasma potassium concentration, the autopsy finding of a large suprarenal, cortical adenoma was unexpected Clini cally there had been no suspicion of a mineralocorticoid excess

Probably the coincidence of hypertension and a suprarenal tumor is merely accidental, thus, it has been

demonstrated that in a larger series of autopsies (7) cortical adenomas may be found in a considerable percentage of cases (up to 38 %) Nevertheless it is impressive that Neuhaus (17) showed adenomas to be present in a significantly higher percentage in patients with hypertension as than in non hypertensive persons (38 % versus 20 %)

As a consequence of our experiences from case 4, we may conclude that external chest massage is clearly indicated when the cardiac arrest is caused by a reversible hypokalemia It is remarkable that a hypokalemia of such a degree could be evoked in a diabetic vegetarian by flumethiazide (Rontyl®) in spite of the use of a preparation with a standard potassium content The observation agrees with the clinical impression that this addition of potassium to the tablets offers a false sense of security at least in some patients (18)

A low plasma magnesium concentration has been recorded in primary aldosteronism (15) As seen from fig 4 the plasma magnesium values in this case were moderately elevated slowly approaching normal concentrations during recovery The diagnosis of a secondary potassium deficiency was further supported by the aforementioned results of the combined treatment with potassium salt and spironolactone

Summary

The frequency of concomitant arterial hypertension and hypokalemia is illustrated by a retrospective study of 238 hypertensive patients from three medical wards 152 patients had a measurement of the plasma potassium concentration performed In 18 out of 46 cases with hypokalemia no obvious cause could be found In 15 of these patients the presence of a primary aldosteronism seems to have been excluded by the results of common clinical diagnostic procedures Differential diagnosis is discussed in greater detail on the basis of case reports from the last three patients, all of whom exhibited suprarenal tumors They include one case of Conn s syndrome and two cases with a suprarenal cortical adenoma of uncertain character A fourth case is described with a reversible cardiac arrest evoked by severe hypokalemia as a complication to treatment with flumethiazide

Acknowledgements

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Pulmonary Changes in Acute Experimental Uremia in Rats

By

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Several writers have called attention to the occurrence of pulmonary changes in association with uremia (2, 4, 5 7, 8, 9) Interest has been directed mainly to the typical roentgenological appearance first dealt with by Roubier and Plauchy (11) The pathologic anatomical features have also been repeatedly described (1, 10) Experimental studies on the uremic lung are still few in number (2, 3)

No consistent opinion on the origin of these pulmonary changes has been presented so far The following factors have been considered important in theory increased blood pressure hypertrophy and decompensation of the left ventricle increased capillary pressure in the lungs and increased capillary permeability Alwall et al (2 3) emphasized the importance of fluid retention and thus added another important factor to the pathogenesis They based their view on clinical observations and animal experimentation

It was the purpose of this work to study the pulmonary alterations occurring in connection with acute experimental uremia Attention is also drawn to the possible development of these changes in the absence of hyperhydration and to the effect of hyperhydration and certain substances with effect presumably on the capillaries

Submitted for publication April 17 1964

Material and methods

The series consisted of 60 male Sprague Dawley rats weighing 150—200 g Ligature of both ureters was performed to produce acute uremia The animals were divided into three groups of 20 rats each In the first group operation was performed under ether anesthesia in the second under nembutal anesthesia (Nembutal©), and in the third under local anesthesia Each group was further subdivided into two groups of 10 rats each The animals in one subgroup received intraperitoneal injection of 5 % glucose solution 12 and 24 hours after operation the dose on each occasion representing 0 5 % of the initial weight of the rat No other fluid was given When the rats had died or been killed (36 hours after operation) they were dissected The rats in the second subgroup were treated with intraperitoneal injections of 5 % glucose (0 5 % of initial weight) 12 hours after operation and of

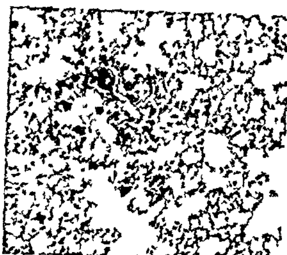


Fig 1 Severe pulmonary change with numerous macrophages and hemorrhage (H & E staining 100 ×)

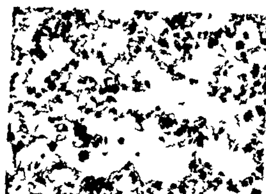


Fig 3 Severe pulmonary change with hemorrhage and numerous macrophages Alveolar walls are thickened and the alveoli contain fibrinous threads (H & E staining 200 ×)

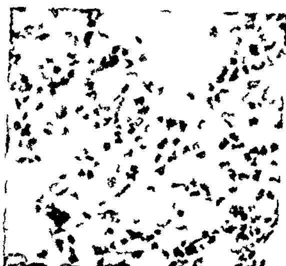


Fig 2 Pulmonary change with marked cellular reaction The alveolar walls are thickened and the alveoli filled with eosinophilic substance (H & E staining 200 ×)

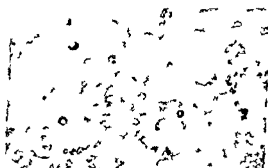


Fig 4 Area with macrophages containing PAS staining granules (H & E staining 200 ×)

Ringer s solution (7 % of initial weight) 24 hours after operation The animals were killed and dissected after 6—12 hours

The lungs of each animal were preserved and fixed in 10 % neutral formaldehyde The specimens were embedded in paraffin and stained by the following methods hematoxylin eosin PAS Perls stain for iron and toluidine blue for acid mucopolysaccharides Frozen sections were stained with Sudan red for lipids

Results

The pulmonary change developing in certain of the animals had the following distinguishing features The lungs were red brown and showed numerous dark violet hemorrhagic areas of variable size Blood colored foam could be expressed from the cut surface Histologic examination (figs 1—4) showed thickening in the alveolar walls which was due to interstitial edema and congestion There was edema around the bronchi and larger blood vessels The alveoli in places showed a large amount of fibrinous weakly eosinophilic substance and homogeneous eosinophilic substance The cel

TABLE I Classification of the pulmonary alterations according to degree of severity

Ether anesthesia				Nembutal anesthesia				Local anesthesia			
Negative	Slight	Moderate	Severe	Negative	Slight	Moderate	Severe	Negative	Slight	Moderate	Severe
No hyperhydration											
1	0	2	7	4	2	2	2	7	0	3	0
Hyperhydration											
0	1	2	7	1	2	1	6	3	4	1	2

lular component in this exudate consisted mainly of red blood cells and large granular cells with clear nuclei as well as cells resembling epithelial cells The granule in the large cells was PAS positive and stained metachromatically with toluidine blue Staining for iron revealed positive granules in very few cells Sections stained for lipids were negative

The changes were considered mild if there was *only* congestion focal bleeding and exudation with a minimal cellular component A moderately severe change was characterized by more extensive changes and a more intense cellular reaction A change was considered severe if it included all the above described features and extended uniformly throughout the whole lung

Table I shows a classification of the pulmonary alterations according to degree of severity

The urea nitrogen was determined on blood samples taken at the moment of death it varied from 150 to 250 mg/100 ml There was *no correlation* between increase in urea *nitrogen* and the pulmonary changes present

Discussion

Experimentally induced acute uremia was associated with pulmonary changes resembling those described in connection with uremia of longer duration (4,5,7, 12) Characteristic features were congestion and edema thickening of alveolar walls the presence of serous and fibrinous exudate in the alveoli the great number of red blood cells and macrophages It is clear that these changes do not make the picture characteristic of uremia but they reflect the general mode of reaction of the lungs in this particular situation

The animals which were operated *on* under local anesthesia and did not receive an excess of fluid could be examined for the possible origin of the pulmonary changes in uremia in the absence of hyperhydration In 3 of the *10 animals in this group a pulmonary* change developed that was considered moderately severe This shows that the syndrome of acute uremia *may itself* include pulmonary changes Owing *to* the fact that the uremic syndrome has so many facets, it is difficult to determine the precipitating factor in the development of the lung changes A reference

point is found in the clinical series of Henkin et al (8), viz a case in which no hyperhydration was noted and peritoneal dialysis without dehydration led to the cure of the pulmonary symptoms It is evident that in uremia there is some factor, remediable with dialysis, which is responsible at least in some of the cases for the production of pulmonary changes

It has been claimed that the increased capillary permeability in uremia causes the flow of protein-rich fluid into the alveoli to be more rapid than the potential outflow (6, 12) It may be assumed that the ether anesthesia used in this work is detrimental to the capillaries of the lungs The results show the decisive effect of this capillary damage under the experimental conditions in the absence of hyperhydration The detrimental factor, in this case a drug, increases considerably the number of cases with pulmonary changes and their degree of severity

The results in the group operated under Nembutal® anesthesia are intermediate as compared with ether and local anesthesia This finding is in agreement with the experiment of Alwall et al (2, 3) on rabbits, in which roentgenologically recognizable pulmonary changes developed more often if the ureteral ligature was made under Narcotal® anesthesia The mechanism of the decisive effect of Nembutal is not known Presumably we are here concerned with retention of a barbiturate derivative or its metabolite with resulting lesion of the capillaries or the heart

The results indicate that hyperhydration increases the incidence and severity of pulmonary changes in each experimental group Though it is not certain that hyperhydration is the primary factor in the pathogenesis it may be concluded that it aggravates existing changes considerably For this reason, in fact, the prevention and correction of hyperhydration is essential from the point of view of therapy On this view, it is possible that overdoses of barbiturates, and ether in particular, should be avoided in uremia

Summary and conclusions

Acute uremia was produced in rats by ligating the ureters under local anesthesia, and under Nembutal® and ether anesthesia The resulting changes, examined histologically, permitted the following conclusions

1 The experimentally induced pulmonary finding was in accordance with the changes previously described in conjunction with uremia
2 Hyperhydration is of decisive importance in the development and aggravation of the pulmonary changes
3 Pulmonary changes may develop as a part of the uremic syndrome without hyperhydration
4 Ether and Nembutal anesthesia increase the incidence and severity of pulmonary changes It is possible that there is here underlying detriment to the capillaries

Addendum

After completion of this work an extensive study on the same subject has appeared *Lindqvist B* Experimental uraemic pulmonary oedema *Acta med scand suppl 418, 1964*

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Klinische und pathologische Beitrage zur posthamodialytischen Diureseverminderung

Erfahrungen mit der Kunstniere vom Type „Necker"

Von

F Rényi Vamos, H Jellinek S Csata und M Toth

Die unmittelbar nach der Hamodialyse auftretende Diureseverminderung gehört an den Kunstnierenabteilungen zu den wohlbekannten Erscheinungen Alwall und Tornberg (1) vertreten die Meinung dass die Ursache hierfur in der nach der Dialyse erfolgenden Verminderung des Blutureaspiegels liegt Aoyama und Kolff (2) konnten die vorubergehende Diuresereduktion bei 6 von 29 dialysierten Kranken feststellen Ihrer Meinung nach — und diese Ansicht vertreten auch Merrill und Mitarb (3) — steht die Abnahme der diuretisch wirkenden Urea im Mittelpunkt des Prozesses

An der Kunstnierenabteilung unserer Klinik haben wir die Diureseverminderung in 22 von 250 Hamodialyse Fallen beobachtet in 15 dieser Fälle war die Verminderung der Harnausscheidung betrachtlich (Abb 1) Als Anurieursachen waren septischer Abort fehlerhafte Bluttransfusion akute Exazerbation einer chronischen Nierenentzundung usw zu verzeichnen

Um die Athiologie zu klaren, wurden folgende Fragen gestellt

1 Ist fur die postdialytische Diureseverminderung die Verminderung des Blutureaspiegels allein verantwortlich?

2 Sind eventuell andere Komponenten nachzuweisen?

Betrachtet man zunachst die Moglichkeit einer neuen Komponente so last sich auf Grund der histologischen Untersuchung eine bejahende Antwort geben Wir unternahmen in 60 anurischen Fallen eine histologische Untersuchung des Nierenexzisats bzw des Sektionsmaterials und konnten feststellen, dass in den 31 Fallen in denen die Biopsie unmittelbar nach der Hämodialyse durchgefuhrt oder in denen der Patient 1—3 Tage nach der Dialyse gestorben war, in zahlreichen Tubuluslichtungen Hamoglobinzylinder in Erscheinung traten (Abb 2) Diese Zylinder lassen sich

Bei der Redaktion am 20 April 1964 eingegangen

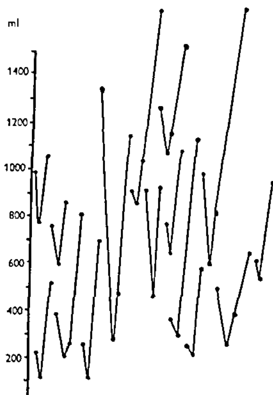


Abb 1 Diureseverminderung nach Hämodialyse mit unserer Kunstniere vom Type „Necker Jeder Punkt bedeutet einen Tag



Abb 2 Hämoglobinzylinder in zahlreichen Tubuluslichtungen

von den übrigen Proteinzylindern leicht differenzieren

Da die erwähnten Gebilde unseres Erachtens teils ein mechanisches Strömungshindernis bilden, teils infolge des mechanischen Druckes das Tubulusepithel schädigen, ist ihnen beim Zustandekommen der postdialytischen Diueresverminderung eine bedeutende Rolle zuzuschreiben Da die postdialytische Diureseverminderung klinischen Angaben gemäss 1—3 Tage lang dauert, kann angenommen werden, dass diese Zeit zur vollkommenen oder partiellen Ausschwemmung der Zylinder nötig ist

Die Entstehung der Hämoglobinzylinder bzw der Ausfall des frei werdenden Hämoglobins sind Folgen der Hämodialyse, da folgende Faktoren, die auf unserer Technik beruhen, verschiedene Grade von Hämolyse hervorrufen können 1 Das Rohrensystem der Kunstniere (Typ Necker) wird mit 1—1,3 l Konservblut aufgefüllt 2 Die extrakorporale Fortbewegung des Blutes besorgen 2 Pumpen Die erythrozytenschädigende Wirkung der Schuster Daleschen Pumpe ist zwar geringgradig, mit einer geringen schädigenden Wirkung muss aber trotztdem gerechnet werden 3 Die während der Dialyse unvermeidliche Manipulation mit den Rohren, Luft- und Gerinnselfiltern kann ebenfalls dazu beitragen, dass ein Teil der Erythrozyten zerstört wird 4 Bei der Dialyse wird insgesamt etwa *600—800 l* Waschflüssigkeit verwendet, deren Zusammensetzung auf Grund der Blutelektrolytwerte bestimmt wird, da jedoch eine vollkommene Isotonie nie erreicht werden kann, trägt auch dieser Faktor zur Entstehung einer geringgradigen Hämolyse bei

Wie ersichtlich, gibt es während der Dialyse mehrere Faktoren, denen bei der Entstehung einer Hämolyse eine Bedeutung zukommt

Es sei allerdings betont, dass wir den Hämoglobinzylindern bei der postdia-

lytischen Diureseverminderung nicht die alleinige Ursache zuschreiben Diese Faktoren sind jedoch für die Verminderung der Harnmenge mitverantwortlich

Aus unseren Ergebnissen geht hervor, dass die Vermeidung von Hamolyse fördernden Faktoren bei der Hamodialyse von ausschlaggebender Wichtigkeit ist

Bezuglich unserer ersten Frage — inwiefern ein niedriger posthämodialytischer Blutureagehalt die Verminderung der Harnausscheidung beeinflusst — sind wir der Meinung, dass diesem unbewiesenen, lediglich vermuteten Faktor keine wesentliche Bedeutung beizumessen ist, da der postdialytische Blutureaspiegel noch immer ziemlich hoch ist

Summary

1 After the dialytic treatment the urinary output becomes often reduced
2 One cause of the reduction is the hemolysis during hemodialysis We used the "Necker" artificial kidney

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Free Fatty Acids of Plasma During Insulin-induced Hypoglycemia in Dog

The Effect of Adrenalectomy and Treatment with Reserpine, Azamethonium and Nicotinic Acid

By

Sven Fröberg Sten Otto Liljedahl and Lars Oro

Many investigations suggest that the sympathetic nervous system is of importance for the mobilization of the free fatty acids (FFA) from adipose tissue to plasma (17 22) The adrenergic neurohormones, norepinephrine and epinephrine injected into man and dog rapidly increase the level of FFA in plasma (7 9 21, 24) The FFA level also increases during different conditions which stimulate the activity in the sympathetic nervous system e g prolonged exercise (2 10) mental stress (4 11) experimental trauma (8) and hypoglycemia (1 35)

To find out if a rise of the FFA level can occur during hypoglycemia without a release of catecholamines from the adrenal medulla the effect of insulin induced hypoglycemia on FFA was studied in adrenalectomized dogs The changes of the FFA levels in the adrenalectomized dogs were compared with the FFA changes in dogs treated with the sympathetic blocking agents, reserpine and azamethonium

The catecholamine stimulated mobilization of FFA in vivo (5, 23) as well as in vitro (6) is inhibited by nicotinic acid The changes of the FFA level during hypoglycemia were therefore also studied in dogs treated with nicotinic acid

Methods

Experimental

The experiments were performed on mongrel dogs weighing between 15 and 34 kg They had fasted at least 20 hours and were anesthetized with Nembutal® (Abbott) Arterial blood samples were withdrawn from an indwelling cathether into heparinized syringes No heparin was injected into the animals Insulin was infused at a constant rate of 0 3 units/kg/body weight per hour during 90 min in all experiments

Four dogs were used as *control* animals Bilateral *adrenalectomy* was performed in four

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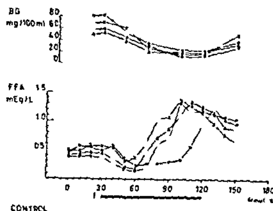


Fig 1 Free fatty acids of plasma (FFA) and blood glucose (BG) during infusion of insulin into four non treated dogs Insulin (I) was infused at a constant rate of 0 3 units/kg/hour from 30 to 120 min as indicated by ———

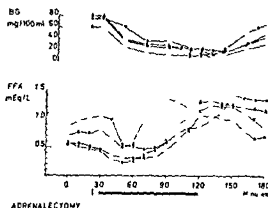


Fig 2 Free fatty acids of plasma (FFA) and blood glucose (BG) during infusion of insulin into four adrenalectomized dogs

dogs They were treated daily with cortison acetate i m 1—2 mg/kg body weight The experiments were performed when at least one week had passed after the operation Four dogs were pretreated with *reserpine* Two doses, each of 0 3—0 4 mg/kg body weight, were injected *i m about 48 and* 24 hours before the experiment Three dogs received *azamethonium i v*, 5 mg/kg body weight 20 min before the infusion of insulin The initial dose was followed by a constant infusion of the drug 0 15 mg/kg/min during the whole experiment.

Four dogs received *nicotinic acid i v*, 200 mg/kg 20 min before the infusion o insulin

Substances

Recrystallized insulin was kindly supplied as Insulin special® from AB Vitrum, Stockholm

Reserpine (Serpasil®) and azamethonium (Pendiom ®) was kindly supplied from AB Ciba, Stockholm

Nicotinic acid was used as a solution of the sodium salt

Analytical

The free fatty acids of plasma were determined according to Dole (12) Blood glucose was determined with the method described by Marks (25)

The statistical analysis were performed according to Snedecor (32)

Results

FFA of plasma during insulin induced hypoglycemia in non treated dogs

When insulin was infused during a period of 90 minutes the mean blood glucose level decreased from 65 to 18 mg/100 ml (fig 1, table I) The level of FFA also decreased in all dogs during the first 20 minutes (fig 1) The mean fall was from 0 46 to 0 23 mEq/l The FFA level then increased in three of the four dogs In the fourth dog the rapid increase of the FFA level did not occur until 70 min after the start of the insulin-infusion The mean increase of the FFA concentration, calculated from the lowest level after 20—40 min to the level at the end of the insulin infusion was 0 94 mEq/l (table II)

FFA of plasma during insulin induted hypoglycemia in adrenalectomized dogs

During the infusion of insulin the mean blood glucose concentration decreased from 74 to 19 mg/100 ml (fig 2, table I)

The FFA level also decreased during the first 20 min (fig 2) The mean fall was from 0 67 to 0 40 mEq/l The FFA level then increased in three of the four dogs In the fourth dog the FFA level did not increase until 50—60 min after the start of the insulin infusion The mean increase of the FFA concentration, calculated from the lowest level after 20—40 min to the level at the end of the insulin infusion was 0 72 mEq/l (table II)

FFA of plasma during insulin induced hypoglycemia in reserpine treated dogs

The mean blood glucose level decreased during the infusion of insulin from 80 to 19 mg/100ml (fig 3 table I) The FFA level also decreased during the first 20 min (fig 3) The mean fall was from 0 55 to 0 25 mEq/l At this point no further change of the FFA level occured (table II)

FFA of plasma during insulin induced hypoglycemia in azamethonium treated dogs

During the infusion of insulin the mean blood glucose concentration decreased from 60 to 14 mg 100 ml (fig 4, table I) The FFA concentration remained almost unchanged in the dogs at a mean level of 0 30 mEq l (fig 4 table II)

FFA of plasma during insulin induced hypoglycemia in nicotinic acid treated dogs

During the infusion of insulin the mean blood glucose concentration decreased from 57 to 17 mg 100 ml (fig 5 table I) The FFA level remained almost unchanged in the dogs at a mean level of 0 30 mEq l (fig 5 table II)

TABLE I The concentration of blood glucose before and at the end of infusion of insulin into non treated and adrenalectomized dogs and into dogs treated with reserpine azamethonium or nicotinic acid respectively (mean and S E of mean)

	No of dogs	Glucose concentration (mg/100 ml) Before the insulin infusion	At the end of the insulin infusion
Control (non treated)	4	65±6	18±2
Adrenalectomy	4	74±6	19±3
Reserpine	4	80±8	19±3
Azamethonium	3	60±3	14±1
Nicotinic acid	4	57±4	17±3

TABLE II Changes in concentration of the free fatty acids of plasma during infusion of insulin into non treated and adrenalectomized dogs and into dogs treated with reserpine azamethonium and nicotinic acid respectively The figures are calculated on the individual changes from the lowest level after 20—40 min of infusion to the level at the end of the insulin infusion (mean and S E of mean)

	No of dogs	Mean change of the FFA concentration (mEq/l)
Control (non treated)	4	0 94±0 11[1]
Adrenalectomy	4	0 72±0 11[1]
Reserpine	4	0 10±0 04
Azamethonium	3	0 04±0 08
Nicotinic acid	4	0 10±0 04

[1] $p < 0{,}01$

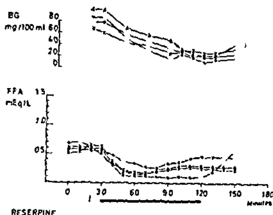


Fig 3 Free fatty acids of plasma (FFA) and blood glucose (BG) during infusion of insulin into four dogs pretreated with reserpine 0 6—0 8 mg/kg body weight

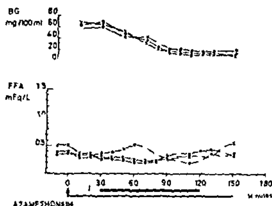


Fig 4 Free fatty acids of plasma (FFA) and blood glucose (BG) during infusion of insulin into three dogs treated with azamethonium Azamethonium was injected i v, 5 mg/kg at ↑ and then 0 15 mg/kg/min at a constant rate

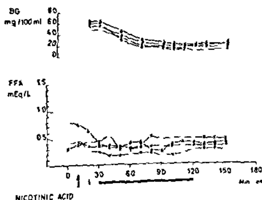


Fig 5 Free fatty acids of plasma (FFA) and blood glucose (BG) during infusion of insulin into four dogs treated with nicotinic acid At ↑ 200 mg/kg of nicotinic acid was injected i v

Discussion

Armstrong et al (1) demonstrated that the level of free fatty acids of plasma in non anesthetized dogs initially decreased and then increased during an infusion of insulin that produced hypoglycemia The same changes of the FFA level were observed in this investigation on anesthetized dogs

By using palmitate 1-C[14] it has been shown that the initial decrease of the FFA level during administration of insulin is due to a decreased mobilization of FFA to plasma (1, 3) Armstrong et al also found that the hypoglycemia induced rise of the FFA level was due to an enhanced mobilization of FFA to plasma This rise was inhibited in dogs pretreated with sympathetic blocking agent, dibenzyline or guanethidine The results therefore suggested that the mobilization of FFA was caused by the increased activity in the sympathetic nervous system that is produced by hypoglycemia (15, 20) In this investigation the same qualitative changes of the level of FFA and blood glucose were observed in adrenalectomized dogs as in intact dogs The results indicated that the mobilization of FFA during hypoglycemia can occur without a release of catecholamines from the adrenal glands

The changes of the FFA level during hypoglycemia were also studied in dogs treated with the sympathetic blocking agents, reserpine and azamethonium

Reserpine depletes the catecholamines from the adrenergic nerves in different organs including the adrenal glands (36) The norepinephrine in adipose tissue

also disappears (26, 33) In the dogs used in this investigation it was confirmed with the histochemical method described by Hillarp (16), that the dose of reserpine that was given depleted the catecholamines from the adrenergic nerves (Wirsén, to be published) In the reserpine treated animals no significant increase of the FFA level was observed although the insulin infusion produced the same degree of hypoglycemia as in the control animals The ganglionic blocking agent, azamethonium also prevented the increase of the FFA level Werk et al (35) reported that a similar substance, hexamethonium only partly inhibited the hypoglycemia induced rise of the FFA level in man However, they studied the late increase of the FFA level after a single injection of insulin when the blood glucose concentration was returning to the initial state

Hypoglycemia does not only increase the secretion of catecholamines but also the plasma concentration of other hormones such as 17 hydroxycorticosteroids (35) growth hormone (19) and glucagon (34) As these hormones influence the FFA mobilization (29) it cannot be excluded that the mobilization of FFA during hypoglycemia was stimulated by hormones other than catecholamines

The presence of corticosteroids seems to be necessary for the effect of catecholamines (34) Some authors have also reported that corticosteroids and ACTH per se increase the level of FFA (13 27) However in anesthetized dogs neither hydrocortisone nor ACTH affected the FFA level (Hydrocortison 40 mg or 0 25 mg of a synthetic ACTH preparation (CIBA 30920 Ba) was injected i v into anesthetized dogs weighing about 20 kg Arterial blood samples were taken at 10 min interval for analysis of FFA No change of FFA level was observed within 180 min (Carlson & Oro, unpubl observations)) The experiments on the adrenalectomized dogs also preclude an acute release of corticosteroids being of significance for FFA mobilization during hypoglycemia

Laurell and Christensson (24) found no effect with growth hormone of pig origin on the FFA level in man but Raben and Hollenberg (28) reported that human as well as simian growth hormone increased the level of FFA in man and dog *Growth hormone* also increased the FFA concentration in rat (14) This effect, however, was not inhibited in rats pretreated with *reserpine* in contrast to the hypoglycemia induced mobilization of FFA *in dog* *Glucagon* stimulates the lipolysis and release of FFA from adipose tissue in vitro (29) and probably also the FFA release *from* adipose tissue in vivo (13, 30) When adipose tissue was taken *from* rats pretreated with reserpine the effect of glucagon on the FFA release was diminished (27) In dog not only the catecholamine depleting drugs reserpine and guanethidine but also the ganglionic blocking agent azamethonium effectively inhibited the hypoglycemia induced rise of the FFA level It is therefore possible that the enhanced mobilization of FFA during hypoglycemia is produced by the increased activity in the sympathetic nervous system As the level of FFA is also increased in adrenalectomized dogs the extra adrenal part of the sympathetic

nervous system may be of importance for this effect on FFA

The catecholamine stimulated lipolysis and FFA release from adipose tissue *in vitro* is inhibited by nicotinic acid (6) The increase of the FFA level during infusion of catecholamines (5, 9, 18, 23), prolonged exercise (10) and mental stress (11) is also inhibited by nicotinic acid In this instance nicotinic acid, like the sympathetic blocking agents, prevented the hypoglycemia induced mobilization of FFA It is therefore possible that nicotinic acid also inhibits the mobilization of FFA stimulated by the catecholamines released from peripheral sympathetic nerve endings However, nicotinic acid does not act specifically on the catecholamine stimulated FFA mobilization as the effect of ACTH and glucagon on the lipolysis in adipose tissue also is inhibited by nicotinic acid (Bally, personal communications)

Summary

The changes in the concentration of free fatty acids of plasma during insulin-induced hypoglycemia have been studied in anesthetized dogs After an initial decrease the FFA level increased significantly in intact as well as in adrenalectomized dogs In dogs treated with nicotinic acid or with the sympathetic blocking agents, reserpine and azamethonium, no increase of the FFA level was observed

The results indicated that an increase of the FFA level can occur during hypoglycemia without a release of catecholamines from the adrenal glands

The role of the extra adrenal part of the sympathetic nervous system for the hypoglycemia-induced mobilization of FFA is discussed

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Myocardial Infarction During Long-term Anticoagulant Therapy

By

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Anticoagulant therapy is widely used to prevent myocardial infarction in several groups of patients The efficacy of this treatment must ultimately be judged from controlled clinical trials Conflicting results of such studies have been published but it is fair to conclude that anticoagulant therapy has some protective effect in many patients The magnitude and duration of this effect are still under discussion

Some insight in this problem can also be gained from a study of patients who develop myocardial infarction during anticoagulant therapy Generally such patients are considered to be therapeutic failures but it is important to answer the question was the failure due to inadequate therapy or did adequate therapy fail to protect against the infarction? If the latter is true a second question must be answered why did the therapy fail?

The purpose of this paper is to report a study of 50 consecutive incidents of myocardial infarction in 45 patients during anticoagulant therapy The adequacy of this therapy has been evaluated, and the autopsy results have been correlated with the quality of the anticoagulant therapy in the 15 patients who died

Methods

The patients were admitted to Medical Department VII Ullevål Hospital Oslo, during the period from August 1961 to April 1963 Every patient who developed a myocardial infarction during anticoagulant therapy was included in the material The following was recorded daily for at least three days after admission presence or absence of pain shock and friction rub, fever leukocytes ESR SGOT and ECG with 12 leads Clinical observation was continued for 3—5 weeks and autopsy was carried out in all patients who died

The *diagnosis* of recurrent myocardial infarction is often difficult. The diagnostic criteria have been discussed in previous publications from this department (6 7 8) We have listed our findings in table I and

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TABLE I Frequency of symptoms, signs, laboratory and ECG findings in 50 cases of acute myocardial infarction (39 of these were recurrent infarctions)

Symptoms	%
Typical anginal pain	100
SGOT > 50 units	88
ESR increase > 10 mm/h	62
Fever > 38°C	60
Leukocytes > 10,000/mm³	40
Shock	38
ECG unchanged	36
ECG Q wave	32
ECG ST-T changes	32
Friction rub	10

TABLE II Indication for and duration of the anticoagulant therapy The figures in parentheses give the range

Indication	Sex	No of pat	Duration of anticoagulant therapy (months)
Myocardial	♂	24	25 3 (0 5—82)
infarction	♀	10	27 0 (1 5—72)
Angina	♂	6	38 1 (1 5—96)
pectoris	♀	3	28 0 (12—46)
Intermittent	♂	2	40 5 (9—72)
claudication	♀	0	—

we established the diagnosis in the following manner All patients had a severe, persistent, crushing pain in the chest for more than one hour, with no relief from nitroglycerine In addition, the SGOT-value increased to more than 50 units in 44 cases Of the remaining six cases, two developed a Q wave in the ECG Finally, four patients had neither a Q wave nor an increased SGOT-value, but they all died, and an acute myocardial infarction was found at autopsy

At *autopsy*, the myocardium was sliced longitudinally and examined for infarcts A recent infarct was found in every patient The coronary arteries were carefully opened with scissors and searched for thrombi

Anticoagulant therapy All patients were on oral anticoagulant therapy with phenylindanedione or dicoumarol Except for two patients who developed myocardial infaction during admission to the hospital, all patients lived at home, and the therapy was administered by their own physician, usually an internist The therapy was controlled by the PP test (12) or by the Thrombotest of Owren (11), later referred to as the TT test When the diagnosis had been established, we obtained from the patient's physician all his data on the anticoagulant therapy, i e, the results of the blood tests and the dosages recommended In the hospital, a TT test was carried out as soon as possible after admission, and the anticoagulant therapy was continued

Material

Sex and age The material consists of 50 infarctions in 45 patients, three men and two women had two infarctions each during the observation period There were 32 men and 13 women For the following calculations we have used the data from the first admission for the five patients who had two infarctions The mean age for the men was 61 5 (44—81) years, for the women it was 62 6 (47—72) years, and for the whole group it was 61 9 years

Weight The height in cm minus 100±10 kg may be considered a liberal normal weight, 32 patients were in this group Four patients weighed less than this and 9 patients weighed more

Hypertension Seven patients had a blood pressure consistently above 160/110 mm Hg

Cholesterol The serum cholesterol was measured on the day of admission The median value and range for all patients was 303 (202—683) mg % Two patients had xanthomatosis with cholesterol values of 524 and 683 mg %

Size of the heart The hearts of those who died weighed more than 400 g at autopsy and

TABLE III Clinical data on 5 patients who had 2 infarctions in the observation period (data from second admission)

Sex	Age	Infarction no	Over weight[1]	Hyper tension[1]	Cholesterol (mg%)	Relative vol of the heart (ml/sqm)
♂[2]	53	3	No	No	329	—
♂	79	3	Yes	No	376	600
♂	67	2	No	Yes	224	600
♀	72	4	Yes	Yes	215	510
♀	64	2	No	No	354	590

[1] See definition in text
[2] This patient died his heart weighed 590 g

TABLE IV The TT level on admission (50 infarctions in 45 patients) The patients who died are subdivided according to whether or not they had a coronary thrombosis

	No of patients with a TT level (%) of					Mean TT (%)
	<10	10–20	21–25	26–30	>30	
All 50 infarctions	3	14	9	5	19	29 4
15 deaths						
9 with recent thrombus	–	1	1	3	4	36 4
2 with partly organized thrombus	–	–	1	–	1	34 5
4 with no thrombus	1	1	1	–	1	21 8

were thus enlarged Of those who survived 7 men and 5 women had an increased relative volume of the heart (over 540 ml/sq m body surface for men and over 490 ml/sq m body surface for women (1)) at X ray examination 3–5 weeks after the infarction Sixteen patients had a relative volume within normal limits and two women had not been examined

Indication for and duration of anticoagulant therapy Table II gives this information The main indication was myocardial infarction 3 men and 2 women had suffered two previous infarctions, and 2 women had three previous infarctions

Five patients had two infarctions during the period of observation Table III shows that they may all be considered poor risks.

Evaluation of the anticoagulant therapy

The anticoagulant level on admission Table IV gives the TT values determined as soon as possible after admission It is difficult to determine the onset of the infarction, but we have presumed that it started when the patient first felt a severe pain On an average the TT test was carried out 15 4 (4—72) hours after the onset. Table IV shows that 17 patients had a TT level below 21 %, 26 had a level below 26 % and 31 had a level below 31 % The average TT level was 29 4 (6—64) % with a standard deviation of 14 7 %

The anticoagulant level on the last examination before the infarction From the physicians records we obtained the results of the last TT-

TABLE I Frequency of symptoms, signs, laboratory and ECG findings in 50 cases of acute myocardial infarction (39 of these were recurrent infarctions)

Symptoms	%
Typical anginal pain	100
SGOT > 50 units	88
ESR increase > 10 mm/h	62
Fever > 38 C	60
Leukocytes > 10 000/mm³	40
Shock	38
ECG unchanged	36
ECG Q wave	32
ECG ST T changes	32
Friction rub	10

TABLE II Indication for and duration of the anticoagulant therapy The figures in parentheses give the range

Indication	Sex	No of pat	Duration of anticoagulant therapy (months)
Myocardial infarction	♂	24	25 3 (0 5—82)
	♀	10	27 0 (1 5—72)
Angina pectoris	♂	6	38 1 (1 5—96)
	♀	3	28 0 (12—46)
Intermittent claudication	♂	2	40 5 (9—72)
	♀	0	—

we established the diagnosis in the following manner All patients had a severe, persistent, crushing pain in the chest for more than one hour, with no relief from nitroglycerine In addition, the SGOT value increased to more than 50 units in 44 cases Of the remaining six cases, two developed a Q wave in the ECG Finally, four patients had neither a Q wave nor an increased SGOT value but they all died, and an acute myocardial infarction was found at autopsy

At *autopsy*, the myocardium was sliced longitudinally and examined for infarcts A recent infarct was found in every patient The coronary arteries were carefully opened with scissors and searched for thrombi

Anticoagulant therapy All patients were on oral anticoagulant therapy with phenylindanedione or dicoumarol Except for two patients who developed myocardial infaction during admission to the hospital, all patients lived at home, and the therapy was administered by their own physician usually an internist The therapy was controlled by the PP test (12) or by the Thrombotest of Owren (11), later referred to as the TT test When the diagnosis had been established, we obtained from the patient s physician all his data on the anticoagulant therapy, i e, the results of the blood tests and the dosages recommended In the hospital, a TT test was carried out as soon as possible after admission and the anticoagulant therapy was continued

Material

Sex and age The material consists of 50 infarctions in 45 patients, three men and two women had two infarctions each during the observation period There were 32 men and 13 women For the following calculations we have used the data from the first admission for the five patients who had two infarctions The mean age for the men was 61 5 (44—81) years for the women it was 62 8 (47—72) years, and for the whole group it was 61 9 years

Weight The height in cm minus 100 ± 10 kg may be considered a liberal normal weight, 32 patients were in this group Four patients weighed less than this and 9 patients weighed more

Hypertension Seven patients had a blood pressure consistently above 160/110 mm Hg

Cholesterol The serum cholesterol was measured on the day of admission The median value and range for all patients was 303 (202—683) mg % Two patients had xanthomatosis with cholesterol values of 524 and 683 mg %

Size of the heart The hearts of those who died weighed more than 400 g at autopsy and

TABLE III Clinical data on 5 patients who had 2 infarctions in the observation period (data from second admission)

Sex	Age	Infarction no	Over weight[1]	Hyper tension[1]	Cholesterol (mg%)	Relative vol of the heart (ml/sqm)
♂[2]	53	3	No	No	329	—
♀	79	3	Yes	No	376	600
♂	67	2	No	Yes	224	600
♀	72	4	Yes	Yes	215	510
	64	2	No	No	354	590

[1] See definition in text

[2] This patient died his heart weighed 590 g

TABLE IV The TT level on admission (50 infarctions in 45 patients) The patients who died are subdivided according to whether or not they had a coronary thrombosis

	No of patients with a TT level (%) of					Mean TT
	<10	10–20	21–25	26–30	>30	(%)
All 50 infarctions	3	14	9	5	19	29 4
15 deaths						
9 with recent thrombus	—	1	1	3	4	36 4
2 with partly organized thrombus		—	1	—	1	34 5
4 with no thrombus	1	1	1	—	1	21 8

were thus enlarged Of those who survived 7 men and 5 women had an increased relative volume of the heart (over 540 ml/sq m body surface for men and over 490 ml/sq m body surface for women (1)) at X ray examination 3—5 weeks after the infarction Sixteen patients had a relative volume within normal limits and two women had not been examined

Indication for and duration of anticoagulant therapy Table II gives this information. The main indication was myocardial infarction 3 men and 2 women had suffered two previous infarctions, and 2 women had three previous infarctions

Five patients had two infarctions during the period of observation Table III shows that they may all be considered poor risks

Evaluation of the anticoagulant therapy

The anticoagulant level on admission Table IV gives the TT values determined as soon as possible after admission. It is difficult to determine the onset of the infarction but we have presumed that it started when the patient first felt a severe pain On an average the TT test was carried out 19 4 (4—72) hours after the onset. Table IV shows that 17 patients had a TT level below 21 %, 26 had a level below 26 % and 31 had a level below 31 % The average TT level was 29 4 (6—64) % with a standard deviation of 14 7 %

The anticoagulant level on the last examination before the infarction. From the physicians records we obtained the results of the last TT-

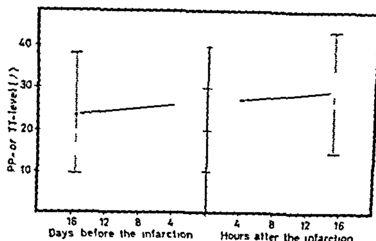


Fig. 1. PP- or TT-level before and after the infarction. The figure gives the mean and the S.D. of the last determination before and of the first determination after the infarction.

or PP-test before the infarction. On an average, this test was carried out 15.8 (1—58) days before the infarction, and the mean of the 50 tests was 23.9 (6—67) % with a standard deviation of 14.6 %. Thus, the level on admission was on an average 5.5 % higher than the last preinfarction level. This difference is significant (0.05 > p > 0.01) as tested by Wilcoxon's matched pairs signed ranks test; this test was performed as described by Siegel (13). Fig. 1 illustrates this finding.

The quality of the anticoagulant therapy before the infarction. We have attempted to evaluate this in two ways.

First, we have collected all the TT- or PP-levels for all the patients from the physicians' records. Table V (third line) shows that a fair number of these tests were outside an even modest therapeutic range: 38 % of the tests were above 25 %, and 26 % of the tests were above 30 %. These results indicate that our patients had not been ideally treated, but they do not tell whether they had been less well controlled than their fellow patients on anticoagulant therapy who did *not* develop myocardial infarction. However, it is possible to find out whether they had been less well controlled than the *average* patient on anticoagulant therapy. Borchgrevink (5) grouped over 10 000 TT- or PP-tests from outpatients on anticoagulant therapy in Oslo. Table V shows that our patients had been better controlled than the outpatients in the medical

TABLE V. Quality of anticoagulant therapy: a comparison of the present material with 3 previously reported materials

Material	Distribution of the PP- or TT-values (%) <10	10–24	>25	>30	Mean PP- or TT-value (%)
Present material					
On admission	6	46	48	38	29.4
Last test before admission	8	60	32	26	23.9
All tests during treatment period	8	54	38	26	24
Borchgrevink (5)					
7 medical departments	4	41	55	41	28
4 internists	6	65	29	17	21
Borchgrevink (4)	12.9	—	—	11.3	19
Bjerkelund (3)	8	—	—	18	—

departments but not quite as well as the patients who were controlled by the practising internists Bjerkelund's (3) and Borchgrevink's (4) own patients were also better controlled than our patients Thus we conclude that our patients had received a fairly average therapy *by present standards in Oslo* Table V also shows that the last test before admission (second line) agreed well with the average level during the entire treatment period while the test on admission (first line) was higher

Secondly, we have studied each patient's record and rated the intensity of his treatment as *high* (if 30 % or less of the TT or PP values were above 30 %) as *medium* (if 30—60 % of the values were above 30 %) or as *low* (if 60 % or more of the values were above 30 %) Table VI shows that 64 % of our patients had received intensive therapy according to these criteria, as compared with 30 % of Waaler's (14) or 94 % of Borchgrevink's (4)

Table VI Quality of anticoagulant therapy evaluation of each patient (data from physicians records) compared with those of Waaler (14) and Borchgrevink (4)

Material	No of pat.	Intensity of therapy (% of patients) High[1]	Medium[2]	Low[3]
Present	45	64	32	4
Waaler (14)	275	30	55	15
Borchgrevink (4)	103	94	6	0

[1] < 30 % of the TT or PP values above 30 %
[2] 30—60 % of the TT or PP values above 30 %
[3] > 60 % of the TT or PP values above 30 %

Table VII gives the pertinent data for the 15 patients who died As compared with the survivors, they were less frequently overweight and tended to have higher cholesterol values

At autopsy they all had enlarged hearts and an acute myocardial infarction A recent thrombus was found in the coronary tree in 9 patients 2 had an older and partly organized thrombus, and 4 had no thrombus Clinically there was no difference between patients with and patients without thrombus (fever leukocytosis ESR SGOT value shock friction rub Q wave)

The TT level on admission was slightly higher in this group than in the group that survived (table VII) The TT level appeared to be lower in those who did not have a thrombus (mean 21 8 %) than in those who

Table VII The patients who died compared with those who survived

	Dead	Survivors
No of pat	15	30
Women/Men	3/12	10/20
Age (years)	62 4 (5? 81	61 3 (44—81)
Overweight (no of pat.)	1	8
Hypertension (no of pat)	3	4
Cholesterol (mg%)	321 (215 683)	303 (202—524)
Duration of anticoagulant therapy (months)	26 8 (3 56	30 1 (0 5—96)
TT ( ) on admission	3?2	[1]28 2
Heart weight at autopsy (g)	543 (410 780)	—

[1] 35 infarctions in 30 patients.

had (mean 36 4 %), (table IV) However, the groups are too small for statistical evaluation

The intensity of the previous anticoagulant therapy as judged from the physicians' records was the same in those who died as in the survivors In this respect there was also no difference between those who died with a coronary thrombosis and those who died without

Discussion

This report is not based on highly selected patients treated by highly specialized physicians We purposely studied a consecutive series of patients who were receiving ordinary medical care in Oslo

The average TT-level on admission was 29 4 % In a similar group of 107 patients collected in the Medical Department VIII of the same hospital, Nordoy (10) found a mean PP level on admission of 29 % However, we found that the TT-level on admission was significantly higher than the last TT- or PP value determined before the infarction The TT-test has almost completely replaced the PP-test for outpatients in Oslo, and, further, the two tests give similar results (11) We do not believe, therefore, that this difference is due to technical variations Several factors may explain such a difference the patients may be too sick to take their tablets, they may vomit, and severe stress may have an effect Cardiac failure with decreased liver function, on the other hand, would tend to decrease the TT-level on admission

It might also be argued that the difference reflects an "escape" from the treatment, an "escape" which directly caused the infarction The difference (5 5 %) is too small to support this argument, and Bjerkelund (3) and Nordoy (10) also concluded from their studies that recurrent infarction was not due to an acute rise in the PP-level These authors suggested that anticoagulant therapy had little or no effect since the PP-level was the same in those patients who developed an acute infarction as in those who did not However, this problem is extremely complex, and at least two important factors should be considered The first is the fact that many patients die of acute myocardial infarction without coronary thrombosis The present findings suggested that the TT-level might be higher in those who died with a coronary thrombosis than in those who died without, and we have confirmed this observation in a subsequent study (9) This finding suggests that adequate anticoagulant therapy offers *some* protection against a *thrombotic* death

Secondly, the duration of therapy must be considered Our patients, like those of Bjerkelund (3), had been treated for a long time The therapy obviously did not protect them when they finally developed an infarction, but it may still have protected them at an earlier stage of the disease Certainly, the controlled studies of Bjerkelund (2), British Medical Research Council (15) and Borchgrevink (4) suggest that this may be true

It should be stressed, however, that coagulation is by no means the only factor involved in the pathogenesis of myocardial infarction untreated pa-

tients may die of myocardial infarction without coronary thrombosis, and some patients (also in the present material) die with coronary thrombosis in spite of vigorous therapy. The question is therefore not whether a coronary thrombosis *can* form in an adequately treated patient, the question is whether this occurs less frequently in such patients than in untreated patients. Both the controlled clinical studies and our autopsy studies suggest that this is so.

Our patients had received an anticoagulant therapy which was close to the average standard in Oslo (table V). Bjerkelund (3), following his own patients, also concluded that the anticoagulant therapy had not been less satisfactory in patients who developed infarction during therapy than in those who did not. However, it is clear that the average therapy, at least in Oslo, is far too modest. The concept of "therapeutic range" is unfortunate, because the practical result of this concept is not that the mean anticoagulant level is in the middle of the range: it is always close to the upper border. Therefore this concept should be discarded and one should aim for a "therapeutic goal" close to the border of safety. Borchgrevink (5) has shown that a TT level of 15 % is certainly not a dangerous goal.

Summary and conclusions

We have studied the clinical history and the quality of the anticoagulant therapy in 45 patients who developed 50 infarctions during anticoagulant therapy. The average duration of anticoagulant therapy was 29 months. The patients' records indicated that their previous anticoagulant therapy had not been less satisfactory than the average therapy in Oslo. The average TT level on admission was 29.4 %, the average value of the last test before the infarction was 23.9 %. This difference is significant, but it is too small to justify the conclusion that recurrent infarction is usually caused by an "escape" from the anticoagulant therapy. Fifteen patients died and were autopsied: nine had a newly formed coronary thrombosis, two had a partly organized thrombosis, and four had not thrombosis. The TT level was higher in those who had thrombosis. This observation has been confirmed in a subsequent study (9).

The value of anticoagulant therapy cannot be judged from this study. We can only conclude that our patients had probably not been less intensively treated than their fellow patients who did not develop infarction, that this therapy is far from optimal, and that the patients who died with coronary thrombosis appeared to have a higher TT level on admission than those who died *without* such a thrombosis.

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Respiratory Activity of Mitochondria from Human Skeletal Muscle before and after Insulin Administration

By

C -G Lundquist and A Svanborg

Most of those cellular activities which are stimulated by insulin, for instance the transport of glucose and other sugars through cell membranes the synthesis of glycogen and the incorporation of amino acids into protein are processes requiring energy which must be furnished by an efficiently functioning mitochondrial system (1)

The main energy suppliers of the cell are the mitochondria in which the process of oxidative phosphorylation takes place As insulin stimulates energy requiring processes it seems reasonable to assume that somehow it primarily stimulates the formation of adenosine triphosphate There is evidence for a direct effect of insulin on mitochondrial activity Lee and Wieseman (7) have shown that intravenously injected insulin labeled with ^{131}I is firmly bound to rat liver mitochondria Hall et al (5) found that the oxygen consumption of liver mitochondria from insulin-deficient rats (alloxan diabetes) is significantly depressed They also found an even greater depression in the formation of adenosine triphosphate

In the present study we have compared the respiratory activity of muscle mitochondria in human diabetics and in non diabetics before and after insulin administration in vivo or in vitro

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Experimental

Three patients with diabetes and *three non diabetic* patients without signs of any metabolic disease were investigated *in connection* with abdominal operations The diabetics had been treated with a diet very similar to the conventional Swedish diet, excluding sugar and sweet foods and with a moderate *restriction* of bread and potatoes

The muscle biopsies were taken from the abdominal wall Before the operation all patients were treated identically except that the diabetics, in order to prevent ketosis were given 16 I U of insulin in 1 000 ml of 5 5 % glucose solution by i v infusion This was started early in the morning on the operation day and was infused slowly *over* about 6 hours One hour before the operation the patients got 1 *ml of* hydromorphine scopolamine All patients except case 6 were

anesthetized with Evipal, succinyl choline, d-tubocurare and nitrous oxide. In order to determine the effect of these agents upon mitochondrial activity, case 6 was given only extradural block with mepivacaine.

In each series of patients one was operated upon because of gallstones, one because of colonic disease and one because of intermittent claudication in the legs.

Case reports

Case 1. A 53-year old man with diabetes known since 14 years. During the last 4 years treated with tolbutamide 0.5 g twice daily. Operated upon because of gallstones. Liver-function tests gave normal results.

Case 2. A 76 year-old man with diabetes discovered 9 years previously. Treated with 32 I.U. of insulin (Novo lente). In 1960 operated upon because of carcinoma of the rectum, this being removed and a colostomy made. There have been no signs of recurrence or spreading of the tumor. The present operation was a revision of the colostomy.

Case 3. A 70 year old woman with diabetes since 1952. Treated with 44 I.U. of insulin (Novo lente). The present operation was a lumbar sympathectomy because of advanced arteriosclerosis and intermittent claudication.

Case 4. A 48-year-old woman operated upon because of gallstones.

Case 5. A 71 year old woman undergoing a resection of the colon because of diverticulosis.

Case 6. A 52 year old man undergoing removal of an arterial occlusion in the right pelvic artery which had caused intermittent claudication.

Preparation of mitochondria

All muscle biopsies were taken from rectus abdominis in connection with surgical interventions. The first biopsy was taken immediately after the patient had been anesthetized. Shortly afterwards insulin (8—12 I.U. of crystalline insulin, Vitrum Sweden) was given intravenously together with 100 ml 5.5 % glucose during 10—15 min. 30—45 min. after the insulin glucose infusion the second biopsy was performed. In case 3 only one biopsy was performed and 0.002 I.U. of an insulin preparation (Insulin Vitrum, Special), recrystallized 4 times and diluted to 0.005 ml with phosphate buffer (pH 7.4), was added to the incubation medium.

Mitochondria were prepared as described by Ernster et al. (3). The muscle specimens were homogenized in an all glass Potter Elvehjem homogenizer. A buffer containing potassium chloride and tris(hydroxymethyl) aminomethane buffer (pH 7.4), described by Chappel and Perry (2), was used as a homogenizing medium. The homogenate was diluted with tris-potassium chloride buffer to a final concentration of 1 g muscle per 10 ml. The homogenate was centrifuged in a Phywe refrigated centrifuge at 700 × g for 10 min. The supernatant was decanted and re-centrifuged at 10 000 × g for 20 min. The mitochondria was washed with tris potassium chloride buffer and recentrifuged as above. Finally the mitochondrial pallet was washed 3 times with 0.25 M sucrose. The mitochondria were suspended in 0.25 M sucrose to a final concentration such that mitochondria from 1 g muscle (wet weight) were in 1 ml of suspension. All operations were performed at 0—3° C. The purity of the mitochondrial preparation was checked by electron microscopy. No contamination by other cellular particles was observed.

The mitochondrial respiration was determined in Warburg vessels in the presence and in the absence of hexokinase. The equilibration time was 5 min. and the temperature of the bath 30° C. Each manometer-vessel contained 1 ml of the mitochondrial suspension, 0.15 ml of pyruvate 0.3 M plus 0.05 ml of malate 0.1 M, 0.3 ml of glucose 3 %, 0.15 ml of phosphate buffer 0.5 M, pH 7.4, 0.1 ml of Mg^{++} 0.1 M, 0.4 ml of sucrose 0.25 M, 0.25 ml of adenosine triphosphate 0.03 M, hexokinase (Sigma grade III) when present, 1 mg. In the centre well was put 0.2 ml of 2 M KOH.

TABLE I Respiration of skeletal muscle mitochondria from diabetic and non-diabetic subjects

	Oxygen consumption [μg atoms oxygen (30 min/g muscle weight)]					
Case no	With hexokinase	Without hexokinase	Stimulation by hexokinase (times)	With hexokinase After insulin	Without hexokinase After insulin	Stimulation by hexokinase (times)
1 Diabetic Ins in vivo	6 56	2 16	3 0	10 08	2 29	4 40
2 Diabetic Ins in vivo	5 30	1 47	3 60	7 74	2 80	2 76
3 Diabetic Ins in vitro	9 07	2 31	3 92	9 48	2 64	3 59
4 Non-diabetic Ins in vivo	10 29	1 76	5 84	12 90	1 92	6 71
5 Non-diabetic Ins in vivo	12 84	3 23	3 97	16 77	3 30	5 08
6 Non-diabetic Ins in vivo	10 53	3 93	2 67	12 93	4 31	3 00

Results

The results are summarized in table I It can be seen from the table the mitochondrial oxygen consumption was increased after insulin administration in vivo It also seems as if the diabetics have a lower oxygen consumption than that of the non-diabetics Insulin added in vitro (case 3) did not increase the oxygen consumption In case 6 where no barbituric acid was used for the anesthesia there was likewise an increased oxygen consumption after insulin administration Hexokinase was found to stimulate the respiration 3 times or more which indicates that the oxygen uptake is coupled to a phosphorylation of adenosine diphosphate and that the ATPase activity is low in both preparations.

Discussion

Ernster et al (3) examining the properties of human skeletal muscle mitochondria found that pyruvate in the presence of malate or α ketoglutarate was oxidized at relatively high rates whereas other Krebs cycle metabolites, including pyruvate or malate alone, were oxidized slowly We have therefore chosen pyruvate + malate as substrates in this investigation

A stimulatory effect of insulin on oxygen consumption has been observed with liver mitochondria from insulin deficient rats and cats (5) and in the present study with mitrochondria from skeletal muscles in both non-diabetic and diabetic humans With animal muscle homogenates and with whole

muscle a stimulatory effect of insulin on oxygen consumption has also been reported by other investigators (6, 8) However, our few results for the addition of insulin in vitro disagree with the observations by Hall et al (5)

The stimulation by the glucose-hexokinase system was of the same order of magnitude in the first biopsy as in that taken 30 minutes afterwards This indicates that no ATP-ase activity had become manifest during the preparative procedure

The barbituric acid derivative Amytal has been shown by Ernster et al (4) to suppress all mitochondrial oxidations involving diphosphopyridine nucleotide in rat liver *in vitro* The barbituric acid derivate Evipal in the dosages now used did not have any obvious respiratory depressant action in muscle mitochondria, as the patient who had got only lumbar-anesthesia had an oxygen consumption of the same order of magnitude Furthermore, insulin was found to stimulate the respiration to about the same degree in this case as in the other

Summary

The oxygen consumption of non-diabetic and diabetic human skeletal muscle mitochondria was measured with the Warburg technique Pyruvate + malate was used as the substrate mixture in the presence or absence of glucose-hexokinase as an ADP-regenerating system After insulin administration *in vivo* the oxygen consumption increased in mitochondria both from diabetics and from non diabetic patients

The observation confirms in humans earlier observations in experimental animals that insulin has an effect on mitochondrial respiration This effect was found to be of the same order of magnitude in diabetics and in non-diabetic patients

Acknowledgement

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Behaviour of the Fractions of Serum Alkaline Phosphatase in the Course of Diseases of Liver or Bone

By

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By means of polyvinyl chloride acetate electrophoresis the serum alkaline phosphatase may be separated into as many as three different fractions α_1 α_2 and β_1, which can be determined quantitatively (1, 2) In children and patients with bone disease the β_1 fraction is increased in relation to the α_2 fraction (β_1/α_2 ratio $>$ 1 2) whereas the α_2 fraction is increased in patients with hepatobiliary disease (β_1/α_2 ratio $<$ 0 8) These changes are usually demonstrable only when the total value of alkaline phosphatase is increased

A more detailed study of eight patients in which the results of repeated electrophoretic analyses of the serum alkaline phosphatase were correlated with the clinical cause is reported below

Methods and material

The methods described by Keiding (1) and Nordentoft Jensen (2) were used in the study The series consisted of four men and four women who were studied during admissions to the First and Second Medical University Clinics (Depts C and M) Århus Kommunehospital the Department of Medicine Århus Amtssygehus and the Department of Medicine Skive Amts- og Bysygehus

Submitted for publication April 30 1964

Case reports

Case 1 A man aged 60 with osteo-arthritis of the hip was followed for 24 months Clinical radiographic and laboratory studies during the observation period did not reveal any evidence of hepatobiliary disease or additional bone disease

The results of the electrophoretic separation of the fractions of the serum alkaline phosphatase are shown in table I Eight specimens of serum were analysed in the course of the 24 months The total phosphatase activity was not increased in any of the specimens The α_1 fraction was absent The α_2 fraction varied from 4 5 to 6 7 K A units and the β_1 fraction from 4 0 to 6 9 K A units The β_1/α_2 index varied from 0 67 to 1 26

Case 2 Woman aged 52 A diagnosis of primary biliary cirrhosis was made in 1959 The diagnosis was based on typical biochemical findings and normal bile ducts revealed by exploratory laparotomy

TABLE I Case 1 Osteo-arthritis of the hip Alkaline phosphatase activity in King Armstrong units

		a_1	a_2	β_1	β_1/a_2	Total
Jan	62	0 0	6 7	4 4	0 67	11 1
Feb	62	0 0	5 6	4 0	0 71	9 6
April	62	0 0	4 5	5 4	1 19	9 9
July	62	0 0	4 8	5 3	1 10	10 1
Aug	62	0 0	5 5	6 9	1 26	12 4
May	63	0 0	4 6	5 6	1 22	10 2
Sept.	63	0 0	4 9	5 1	1 04	10 0
Jan	64	0 0	4 9	5 0	1 02	9 9

TABLE II Case 2 Primary biliary cirrhosis Osteomalacia Alkaline phosphatase activity in King Armstrong units

		a_1	a_2	β_1	β_1/a_2	Total
Oct	62	0 3	5 7	12 0	2 09	18 0
		Calcium and vit D therapy				
Nov	62	0 0	7 7	10 8	1 44	18 5
Aug	63	0 0	5 9	5 0	0 84	10 9

TABLE III Case 3 Prostatic cancer with bone metast Alkaline phosphatase activity in King Armstrong units

		a_1	a_2	β_1	β_1/a_2	Total
April	62	3 9	32 8	52 3	1 59	89 0
		Stilboestrol therapy				
June	62	1 6	36 5	63 9	1 75	102 0
		Orchidectomy and diethylstilboestrol				
May	63	0 2	7 4	17 4	2 35	25 0

In 1962, radiography of the spinal column revealed incomplete fractures of the second, third and fourth lumbar vertebrae suggestive of osteomalacia.

From Oct 1962 to March 1963 inclusive, the patient was given 200 000 I U of vitamin D and 3 g calcium phosphate daily, and from April to Aug 1963 300 000 I U of vitamin D and 3 g calcium phosphate daily

Table II shows the results of four electrophoretic analyses in 1962 and 1963 The a_1 fraction was absent The first analysis revealed a β_1/a_2 index of 2 09, due to an increase in the β_1 fraction (12 0 K A units) After treatment with vitamin D and calcium phosphate the index decreased to 0 84 and the β_1 fraction to 5 0 K A units

Case 3 Man aged 70 In 1958, he was subjected to prostatectomy by the method of Freyer because of cancer of the prostate In April 1962, radiography revealed metastases to the spinal column Stilboestrol treatment, 15 mg daily, was commenced in May 1962 Bilateral orchidectomy was performed in March 1963, followed by administration of diethylstilboestrol phosphate 500 mg three times weekly

Table III shows the results of three determinations in 1962 and 1963 Initially, the β_1/a index was 1 59, and the β_1 fraction was estimated as 52 3 K A units After 2 months' treatment with stilboestrol both the index value and the β_1 fraction had increased Orchidectomy and administration of diethyl stilboestrol were followed by a decrease in the β_1 fraction, from 63 9 to 17 4 K A units The accompanying a_2 increase had subsided At the last analysis the index value was 2 35

Case 4 A woman aged 61 was admitted with obstructive jaundice referable to cancer of the head of the pancreas, in Sept 1960 The obstruction was relieved by operation In Nov 1961, steatorrhoea and staphylococcal sepsis were present In Dec 1961, the patient had fever and was in a poor general condition A liver abscess was suspected but exploratory laparotomy did not reveal any abscess

It appears from table IV that the first analysis of the fractions of alkaline phosphatase revealed an index of 0 18 and an a_2 fraction of 25 1 K A units The a_1 fraction was increased both at the first and the second analysis A year after the relief of the

biliary obstruction the α_2 fraction was 7 8 K.A units and the index 0 75 The α_2 fraction was still increased

Case 5 A woman aged 51 was subjected to operation for an adenoma of the parathyroid Radiographic signs of osteitis fibrosa generalisata were present Post-operatively the patient was treated with dihydrotachysterol In July 1962 radiography suggested that the osseous structure was approaching normal

It is seen from table V that at the first analysis of the fractions of alkaline phosphatase in the serum the index was 1 07, and the β_1 fraction amounted to 50 8 K.A units During the next 11 months considerable falls occurred in the α_2 and β_1 fractions, especially during the first two months whereas the index remained unchanged above 1 00 The α_1 fraction was zero throughout the period of observation At the first analysis, the level of the α_2 fraction (47 2 K A units) was considerably higher than that usually observed in association with an increased β_1 value

Case 6 A man aged 54 was admitted with fever and loss of weight and strength

In June 1961 left sided nephrectomy was performed because of hypernephroma After the operation the temperature returned to normal and the general condition improved

In Jan 1962 fever recurred and incipient cachexia was noticed Metastases from the hypernephroma were demonstrated in the lungs The fever persisted the cachexia increased in severity severe anaemia developed and death occurred in Aug 1962 Autopsy revealed local recurrence of the tumour and metastases to the lungs liver and right kidney No bone metastases

Table VI shows variations mainly in the α_1 and α_2 fractions The α_1 fraction varied within wide limits (from 0 to 25 6 K.A units) At the first analysis the α_2 fraction was 14 4 K.A units and the index 0 43 Later the α_2 fraction fell and finally rose from 6 4 to 34 4 K.A units whereas the β_1 fraction remained fairly constant The index value fell to 0 19

TABLE IV Case 4 Obstructive icterus Alkaline phosphatase activity in King Armstrong units

		α_1	α_2	β_1	β_1/α_2	Total
Oct	60	6 3	25 1	4 4	0 18	35 8
Oct	60	Obstruction relieved				
Nov	61	6 1	7 8	5 9	0 75	19 8

TABLE V Case 5 Osteitis fibrosa generalisata Alkaline phosphatase activity in King Armstrong units

		α_1	α_2	β_1	β_1/α_2	Total
Nov	61	Parathyreoid adenoma extirpated				
Jan	62	0 0	47 2	50 8	1 07	98 0
March	62	0 0	11 1	24 4	2 19	35 5
Oct	62	0 2	3 5	5 4	1 56	9 1
Nov	62	0 0	2 7	6 6	2 42	9 3
Dec	62	0 0	2 4	5 8	2 47	8.2

TABLE VI Case 6 Hypernephroma sin. Alkaline phosphatase activity in King Armstrong units

		α_1	α_2	β_1	β_1/α_2	Total
May	61	6 9	14 4	6 3	0 43	27 6
June	61	Nefrectomia sin				
Oct	61	0 0	6 8	6 2	0 92	13 0
Dec	61	0 0	6 4	6 7	1 05	13 1
Jan	62	3 4	7 0	4 8	0 69	15 2
Jan	62	Lung metastases				
April	62	25 6	24 0	8 3	0 34	57 9
May	62	11 5	23 2	5 1	0 22	39 8
June	62	11 4	34 4	6 4	0 19	52 2
Aug	62	Autopsy Liver and lung metastases				

Case 7 Woman aged 52 In 1955 amputation of the left breast with partial excresis of the axilla was performed because of scirrhous carcinoma of the breast with involvement of the axillary lymph nodes Local roentgen irridation was given post-operatively

TABLE VII Case 7 Cancer mammae Bone metastases Alkaline phosphatase activity in King Armstrong units

		α_1	α_2	β_1	β_1/α_2	Total
Jan	62	0 5	7 5	6 9	0 91	14 9
Feb	62	2 3	7 1	8 8	1 24	18 2
June	62	2 1	16 4	35 5	2 05	54 0
Aug	62	Hypophysectomia				
Sept	62	9 3	23 0	7 1	0 31	39 4
Nov	62	Autopsy bone liver and pleural metastases				

TABLE VIII Case 8 Primary biliary cirrhosis Alkaline phosphatase activity in King Armstrong units

		α_1	α_2	β_1	β_1/α_2	Total
April	61	5 4	30 3	14 4	0 48	50 1
Nov	62	2 1	16 3	19 7	1 21	38 1
Nov	62	Steatorrhoea				

In Dec 1961 metastases to the spinal column were confirmed by radiography From March 1962 up to the time of death in Nov 1962, increasing cachexia occurred, accompanied by fever of varying severity Testosterone treatment was given from April to July 1962 Transcranial hypophysectomy was performed in Aug 1962

Autopsy (Nov 1962) revealed metastases to the spinal column, liver, mediastinal and retroperitoneal lymph nodes and pleural and pericardiac carcinomatosis

It is seen from table VII that the first fractionation of alkaline phosphatase showed a near normal β_1 fraction and an index of 0 91 The β_1 activity increased to 35 5 K A units in June 1962 and then fell steeply in relation to the hypophysectomy The α_2 fraction increased in June 1962 and remained unaffected by the hypophysectomy The α_1 fraction increased in Aug 1962, three months before death

Case 8 A woman aged 60, was admitted in April 1961 with primary biliary cirrhosis which was confirmed by biochemical studies of the serum and by histological examination of a biopsy specimen removed from the liver Steatorrhoea was observed in Nov 1962 Radiography failed to reveal any signs of osteomalacia

Table VIII shows that at the first analysis of the serum alkaline phosphatase all the fractions were increased with an index value of 0 48 The next analysis showed an increase in the β_1 fraction and falls in the other two fractions The index had increased to 1 21

Results and discussion

Within a period of 24 months, electrophoretic separation of the alkaline phosphatase was performed on eight different samples of serum obtained from a patient without clinical, laboratory or radiographic signs of liver disease or bone disease other than osteo arthritis of the hip (case 1) Only slight changes in the electrophoretic pattern were observed, and this example is shown to demonstrate the degree of variations occurring in normal subjects

In a previous study, electrophoretic analysis of sera with increased alkaline phosphatase activity showed that if the β_1/α_2 ratio exceeds 1 20, the cause of the increase must be sought in the skeletal system, whereas an index value below 0 80 suggests that the increase in the phosphatase activity is due to hepato biliary disease

In agreement with this observation repeated analyses of serum samples from patients with bone disease showed that falls in the index value and the total

activity of the β_1 fraction occurred in parallel with the subsidence of the bone affection while the α_2 fraction remained unchanged throughout the course (case 2) A considerable fall in the β_1 fraction was revealed in two patients (cases 3 and 5) but likewise for the α_2 concentration, so that the index value remained unchanged In case 8, steatorrhoea occurred simultaneously with an increase in the β_1 fraction and the index value Obstructive jaundice was associated with a low index and a high α_2 fraction (case 4) Relief of the obstruction was followed by a fall in the α_2 fraction while no definite change was observed in the β_1 fraction

In case 6 the development of liver metastases from a hypernephroma without concurrent bone disease was accompanied by an isolated increase in the α_2 fraction an unchanged β_1 fraction and a decreasing index

The combination of liver and bone affection resulted in a more complex situation (case 7) In spite of radiographic signs of bone metastases, the first electrophoretic analysis showed a slight increase in the β_1 fraction and an index of 0 93 In the following analyses β_1 increased to 35 5 K A units and the index to 2 02 After hypophysectomy the β_1 fraction fell to 7 1 K A units and the index to 0 31 During the last seven months of the observation period the α_2 fraction rose from 7 1 to 23 0 K A units — a rise which occurred simultaneously with a fall in the β_1 fraction i e it was not just an accompaniment of an increase in the β_1 fraction In agreement with these observations autopsy revealed both liver and bone metastases

Repeated electrophoretic analyses of alkaline phosphatase in the serum from patients with bone or liver disease thus showed agreement between the electrophoretic pattern of the phosphatase fractions and the clinical, radiographic and biochemical findings Electrophoretic study of the serum alkaline phosphatase may give an unequivocal picture when the total alkaline phosphatase activity is increased However, there is not invariably a time relation between the occurrence of an increased β_1 fraction and a high index on the one hand and radiographic signs of bone metastases on the other Thus, in case 7, radiographic signs were observed before typical changes in the phosphatase pattern occurred These changes were also observed to occur in the reverse order in patients who were studied only once

Both this and a previous study (2) thus show that electrophoretic estimation of the fractions of alkaline phosphatase in the serum is a parameter which indicates whether the cause of the increase in alkaline phosphatase should be sought in an affection of the skeletal or the hepatobiliary system and which may be utilised in the evaluation of the progression or regression of affection of these systems

Summary

In patients with liver or bone disease, repeated electrophoretic analyses of the alkaline phosphatase of the serum revealed a correlation between the variations in the activity of the phosphatase fractions and the course of the disease

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Latent Parathyroid Insufficiency Following Thyroidectomy

By

Th Friis and S Hahnemann

Hypoparathyroidism as a complication to thyroidectomy has been known since 1890 when it was shown by v Eiselberg (4) that tetany might follow upon thyroid operations in man In 1906 Erdheim (5) demonstrated that the tetany was due to operative damage to the parathyroid glands

The reported frequency of clinically manifest parathyroid insufficiency following thyroid operations has ranged from 0 2 % to 5 8 % (10, 18) In a Danish series of 608 patients thyroidectomized for hyperthyroidism during the period 1941—1950 the frequency of tetany immediately after the operation was 1 3 % (17) At follow up of 516 of these patients in 1955 the frequency was 1 1 % (7) Immediately after the operation 9 % had a serum calcium level below 9 mg/100 ml and at follow up 3 6 % Thus the parathyroid insufficiency is often transient (19) The explanation is believed to be hypertrophy of remaining parathyroid tissue restoring a normal serum calcium level (3) Others however, are of the opinion that no notable compensatory hypertrophy of parathyroid tissue can take place (9)

According to some authors, however, parathyroid insufficiency is considerably more common following thyroid operation Under normal circumstances, this will not manifest itself in a reduced serum calcium level until the parathyroid glands are subjected to a negative calcium balance with a consequent tendency to a fall in serum calcium (9, 16, 19) If the serum calcium shows a tendency to fall in such a stres situation, normal subjects secrete more parathormone which mobilizes calcium from the bones restoring the serum calcium level to normal In latent parathyroid insufficiency such a fall in serum calcium does not elicit sufficient parathormone to normalize the serum calcium level as the glands are yielding their maximum under normal circumstances

These aspects have been studied by Davies et al (2) in a series of thyroidectomized persons In a group of 82 one showed tetany and two reduced serum calcium under normal circumstances Otherwise the serum calcium values were normal However the mean values

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were significantly lower than in 80 non-thyroidectomized subjects Following this 19 thyroidectomized persons who had a low normal serum calcium were put on a low-calcium diet and given sodium phytate which binds calcium in the intestinal canal, thus reducing the supply of calcium to the body During this test the serum calcium fell in 11 subjects to below 8 5 mg/100 ml (normal range 8 9—10 8 mg/100 ml) Davies et al feel that the failure of parathormone to respond to the fall in serum calcium is due to a reduction in the blood supply to the parathyroid glands owing to the ligation of the inferior thyroid artery during the thyroidectomy

In a later study, Rose (15) could not confirm these findings, while Jones et al (8), by a somewhat modified technique, claimed to have shown that 13 out of 46 thyroidectomized persons with serum calcium at the lower end of the normal range, had latent parathyroid insufficiency

Material and methods

Since the findings do not appear to be consistent, we felt that it would be of interest to test Davies et al's results in a Danish series The investigation was supplemented by determination of the urinary output of phosphorus assessed by the percentage tubular re-absorption of phosphorus and by the phosphate excretion index (14) in order to assess also the parathyroid function of thyroidectomized subjects on the basis of the phosphaturic action of the hormone

The material comprised 10 (7 female and 3 male) non thyroidectomized, euthyroid patients with non hormonal diseases and 10 (9 female and 1 male) patients who had undergone subtotal thyroidectomy These patients were selected at random, all had normal serum calcium, and none showed definite signs of hypoparathyroidism Lastly, the study included one woman who had exhibited definite signs of tetany following thyroidectomy for hyperthyroidism 21 years previously, but who now showed negative Chvostek and Trousseau signs, while she still had paraesthesiae and reduced serum calcium (3 80 mEq/l) She was untreated when the test was started

Out of the other 10 thyroidectomized patients, 5 had undergone the operation for hyperthyroidism and 5 for non toxic goitre in various hospitals during the period 1942—1963 (5 in surgical department A of the Frederiksberg Hospital) All were euthyroid and had a normal B M R, PBI triiodothyronine uptake by the erythrocytes, and I^{131} uptake by the thyroid gland which could be suppressed by administration of triiodothyronine In 2 (cases 3 and 11), however, there was a reduced B M R and PBI Electrophoresis showed normal serum proteins in all cases No subject was on thyroid hormone medication at the time of the investigation

Technique

In all the cases the test was done in 3 stages

1 On an ordinary hospital diet during a 6 day period
2 On a low calcium diet containing 150 mg calcium daily during a 6-day period and lastly
3 On a low calcium diet plus 9 g sodium phytate daily during a 4 day period All 3 periods were completed in succession without any free intervals

Since we wanted to investigate the effect of a low-calcium diet alone upon the various parameters a daily supplement of 500 mg phosphorus in the form of 1 44 g primary and 0 97 g secondary sodium phosphate was added to the low-calcium diet as it was estimated that the daily phosphorus content of the low calcium diet was about 500 mg below that of the ordinary hospital diet

During the 1st and 2nd periods serum calcium and serum phosphorus determina

tions were done every other day, while the calcium and creatinine content of the 24 hour urine was determined daily During the 3rd period all 4 parameters were determined daily On the average therefore there are 3 or 4 determinations of serum calcium and serum phosphorus in each period, all in duplicate The patients were not fasting when the blood specimens were removed As a criterion of latent parathyroid insufficiency, we demanded a fall in serum calcium to below 4 5 mEq/l during administration of phytate Calcium and phosphorus were determined by the EDTA method (11) and by the method of Muller (12), creatinine by the method of Bonsnes and Taussky (1) The normal range for serum calcium was 4 5—5 5 mEq/l for serum phosphorus 0 9—1 5 mmol/l Fifty serum calcium determinations on normal subjects performed at the time of the investigation revealed a mean value of 4 95 mEq/l ± 0 15 On the last day of each period phosphate and creatinine clearance determinations were carried out from 9 a m —1 p m and from 1 p m — 5 p m by the technique described previously (6) On the basis of the results the tubular re absorption of phosphorus was calculated as a percentage of the amount filtered by the glomeruli (TRP%)

$$TRP\% = \left(1 - \frac{\text{phosphate clearance}}{\text{creatinine clearance}}\right) \times$$

100% (6 and others) and phosphate excretion index (PEI)

$$PEI = \frac{\text{phosphate clearance}}{\text{creatinine clearance}} - (0.055 \times$$

serum phosphorus in mg/100 ml—0 07) (14)

These indices decrease and increase respectively in the presence of increased parathyroid activity Normal range 83—93% and 0 ± 0 07 Lastly electrophoretic determinations were carried out at the beginning and completion of the experimental period

Results

Thus the investigations comprise 5 groups of laboratory data viz 1 serum calcium 2 serum phosphorus 3 the tubular re absorption of phosphorus as a percentage of the filtered amount (TRP%), 4 phosphate excretion index (PEI), and 5 24 hour urine calcium determination including determination of the calcium creatinine index (Ca/creatinine concentration in 24 hour urine) (13) The mean values of these parameters were calculated within each of the 3 experimental periods in the 10 non thyroidectomized and the 10 thyroidectomized patients with normal serum calcium, while the thyroidectomized patient with manifest signs of parathyroid insufficiency is not included in the calculation of the mean values

The results are presented in figs 1—6 and table III Tables I—II give the mean value of the serum calcium determinations in the 1st experimental period (ordinary diet) and the lowest serum calcium determination in the 3rd period (low calcium diet + sodium phytate) as well as the difference between the two

1 *Serum calcium*

A comparison of the values for serum calcium on an ordinary diet with the lowest serum calcium value during administration of phytate in the non thyroidectomized subjects reveals (table I) that in 7 out of 10 there was a decrease The mean decrease was 0 17 ± 0 21 which is barely significant (t = = 2 61 0,05 > p > 0 02) *No value fell to below 4 5 mEq/l* In the 10 thyroidectomized patients without manifest para thyroid insufficiency the decrease was considerably greater and differed significantly from that in the non thyroidectomized subjects 0 42 ± 0 14 (t = = 3 16 0 01 > p > 0 001) The patient

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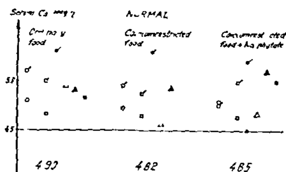


Fig 1 Mean values of serum calcium in non-thyroidectomized on (1) ordinary diet, (2) low calcium diet + 500 mg phosphorus and (3) low-calcium diet + 500 mg phosphorus + 9 g sodium phytate daily

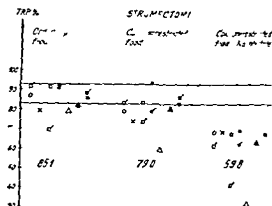


Fig 4 TRP% in thyroidectomized on the three research periods above

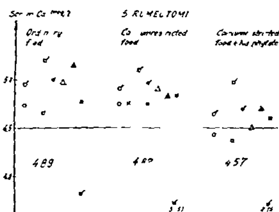


Fig 2 Mean values of serum calcium in thyroidectomized on the three research periods above (■ the patient with parathyroid insufficiency)

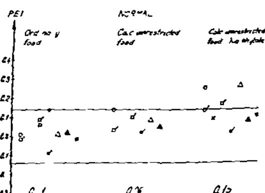


Fig 5 PEI in non thyroidectomized on the three research periods above

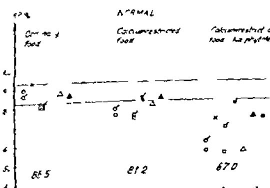


Fig 3 TRP% in non thyroidectomized on the three research periods above

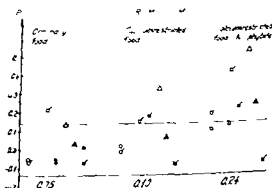


Fig 6 PEI in thyroidectomized on the three research periods above

TABLE I Serum calcium before and during administration of sodium phytate (minimum value) in non thyroidectomized patients

Case		Before low calcium diet (mean value) mEq/l	During sodium phytate (minimum value) mEq/l	Difference mEq/l
1	○	4.80	4.70	−0.10
2	×	4.77	4.90	+0.13
3	□	4.67	4.50	−0.17
4	●	4.65	4.50	−0.15
5	△	4.95	4.50	−0.45
6	▲	4.90	4.90	0
7	■	4.83	4.90	+0.07
8	⌒′	5.10	4.60	−0.50
9	●′	5.30	5.10	−0.20
10	□′	5.00	4.70	−0.30
m ± s		4.90±0.21	4.73±0.21	−0.17±0.21

Symbols as in figs 1, 3 and 5

TABLE II Serum calcium before and during administration of sodium phytate (minimum value) in thyroidectomized patients (case 11 is not included in the calculation of the mean values)

Case		Before low calcium diet (mean value) mEq/l	During sodium phytate (minimum value) mEq/l	Difference mEq/l
1	○	4.73	4.40	0.33
2	×	4.60	4.30	0.30
3	□	4.65	4.30	0.35
4	●	4.85	4.20	0.65
5	△	4.97	4.30	0.67
6	▲	5.15	4.70	0.45
7	■	4.77	4.50	0.27
8	◡′	4.95	4.50	0.45
9	□′	5.20	4.80	0.40
10	●′	5.00	4.70	0.30
(11	■′	3.80	2.60	1.20)
m ± s		4.89±0.20	4.47±0.21	0.42±0.14

Symbols as in figs 2, 4 and 6

with parathyroid insufficiency (table II No. 11) exhibited a greater fall than the other thyroidectomized patients (1.20 mEq/l) who showed a decrease of from 0.27–0.67 mEq/l, *5 to below 4.5 mEq/l*. *In other words* these persons had latent *parathyroid insufficiency*. There was no relationship *between the* magnitude of the decrease and the level of serum calcium on an ordinary diet when disregarding the patient with manifest parathyroid insufficiency.

It should be mentioned that the serum calcium levels in the 2 groups of subjects did not differ from each other on an ordinary diet although they showed differences during administration of sodium phytate.

A look at the alterations in the mean values found in the 2 groups of subjects *within the 3* experimental periods will

TABLE III Mean values and S D of calcium and phosphorus indices in 10 non thyroidectomized and 10 thyroidectomized patients on (1) ordinary diet, (2) low calcium diet + 500 mg phosphorus, and (3) low calcium diet + 500 mg phosphorus + 9 g sodium phytate daily

	Serum calcium	Urinary calcium	Calcium/creatinine index	Serum phosphorus	TRP %	PEI
Non thyroidectomized patients						
(1)	4 90±0 21	260±115	0 232±0 085	1 10±0 19	86 5± 5 4	0 01±0 07
(2)	4 82±0 24	177±136	0 171±0 067	1 19±0 14	81 2± 4 7	0 06±0 06
(3)	4 85±0 22	86± 58	0 083±0 039	1 28±0 18	67 0± 9 6	0 15±0 09
Thyroidectomized patients						
(1)	4 89±0 20	153± 67	0 176±0 094	1 08±0 15	85 1± 7 4	0 05±0 10
(2)	4 82±0 17	132±121	0 082±0 049	1 16±0 20	79 0± 8 8	0 10±0 11
(3)	4 57±0 20	45± 27	0 052±0 034	1 28±0 20	59 8±13 1	0 24±0 14

show that among the non thyroidectomized subjects (fig 1) they rose in 3, remained unchanged in 2, and fell in 5, but never to a level lower than 4 5 mEq/l during administration of phytate On a low calcium diet alone one fell to below 4 5 mEq/l On this diet 6 fell, while 3 rose On the whole, there was no question of a significant fall in the non-thyroidectomized patients (table III), either on a low-calcium diet alone (4 90—4 82 mEq/l) or on sodium phytate (4 90—4 85 mEq/l) On the latter, 2 fell by more than 0 17 mEq — which was the minimum decrease among the thyroidectomized subjects

The mean values of the 10 thyroidectomized subjects during the 3 experimental periods fell by 0 17 mEq/l to 0 50 mEq/l during administration of phytate (fig 2) The patient with manifest parathyroid insufficiency fell by 1 05 mEq/l In the 4 serum calcium fell to below 4 5 mEq/l On a low-calcium diet alone 7 fell, while 3 rose One fell to below the normal range On the whole (table III), there was no significant fall on a low calcium diet alone (4 89—4 82 mEq/l), unlike the findings during administration of phytate (4 89—4 57 mEq/l) In this respect the two groups of patients differed significantly from each other (t = 2 80, 0 02 > p > 0 01) On a low calcium diet alone the values were identical During administration of phytate, the patient with manifest parathyroid insufficiency (table II, No 11) developed positive Chvostek and Trousseau signs and incipient tetany on the last day of the test The other patients showed no signs of tetany, and Chvostek's sign was negative

2 Urinary calcium

The mean value and standard deviation of the analytical results are presented in table III Through the 3 experimental periods the calcium output decreased in both groups (non-thyroidectomized 260—86 mg/24 hours, thyroidectomized 153—45 mg/24 hours) It may be seen that on the average the values were lower in the thyroidectomized patients

The difference was significant on an ordinary diet ($t = 2.39$, $0.05 > p > 0.02$) while it was not quite significant during administration of phytate ($t = 2.02$, $0.1 > p > 0.05$) (table III) The calcium/creatinine index (13) also showed a decrease through the experimental period. In this respect too the thyroidectomized patients were lower, especially on a low calcium diet alone ($t = 3.38$ $0.01 > p > 0.001$)

3 Serum phosphorus

The mean value and standard deviation of the results are shown in table III It is apparent that in both groups the values showed an increasing trend through the 3 experimental periods The two groups did not differ from each other in any of the 3 periods During administration of sodium phytate 2 of the non thyroidectomized and 3 of the thyroidectomized patients were found to be above the normal range

4 Tubular re absorption of phosphorus (TRP%)

The TRP% in the 2 groups of patients is presented in table III and figs 3 and 4 It is evident that the values fell through the 3 experimental periods but surprisingly to an equal extent in both groups It will be noted that the patient with manifest parathyroid insufficiency who incidentally did not have an increased TRP% decreased less than the others Among the non thyroidectomized subjects 3 had values below the lowest normal limit on an ordinary diet while all were reduced during administration of phytate In the thyroidectomized group the corresponding numbers were 4 and 11

5 Phosphate excretion index (PEI)

Since it could not be ruled out that the increasing serum phosphorus through the experimental periods was a contributory cause of the decreasing TRP% (14), the phosphate excretion index was calculated, correcting for the effect of an alteration in serum phosphorus upon the TRP% This is supposed to be a more conclusive expression of parathyroid function measured by the phosphaturic effect (14) The result is shown in table III and figs 5 and 6 It will be seen that the PEI rose through the 3 experimental periods During the phytate period 4 of the non thyroidectomized and 8 of the thyroidectomized patients were above the upper limit of normal (+ 0 14) It will be noted that the patient with manifest parathyroid insufficiency did not exhibit an increase in PEI during the experimental periods The two groups do not differ significantly from each other although the PEI tends to be higher among the thyroidectomized patients especially during administration of phytate ($t = 1.75$ $0.1 < p < 0.05$)

Discussion and conclusion

Our investigations have confirmed Davies et al s (2) findings in so far as 5 out of 10 thyroidectomized patients without manifest parathyroid insufficiency and with normal serum calcium showed a decrease to below 4 5 mEq/l during administration of phytate Three of these 5 subjects had serum calcium levels at the lower limit of normal at the commencement of the test This also accords with the findings of Davies et al

On the other hand, we found no relationship between the magnitude of the decrease and the initial calcium levels, when disregarding the patient with manifest parathyroid insufficiency Unlike Davies et al we found no difference in serum calcium between the two groups of patients before the tests were started A comparison of the decrease in the two groups of subjects shows some overlapping, as the minimum decrease in the thyroidectomized patients was 0 17 mEq/l assessed on the basis of the mean values during administration of phytate, while two of the non-thyroidectomized subjects decreased by more than 0 17 mEq/l In this respect, our results cannot be compared with Davies et al 's, as they had no control serie during administration of phytate

The explanation of the greater decrease in thyroidectomized patients must be a deficient parathyroid hormone reserve, so that calcium cannot be mobilized from the bones According to Davies et al the cause is the ligation of the inferior thyroid artery during the thyroidectomy From this vessel the parathyroid glands derive their main blood supply However, in Jones et al 's (8) material the inferior thyroid artery was not ligated, but they found latent hypoparathyroidism in 13 out of 46 thyroidectomized patients The reason is stated to be ligation of small vessels subcapsularly in the thyroid gland, which might possibly reduce the blood supply of the parathyroid glands Our patients had had their operations in various Danish hospitals, and presumably some of the operations involved ligation of the inferior thyroid artery There was no relationship between the time of operation and the magnitude of the decrease in serum calcium, and it was of no significance to the magnitude of the decrease whether the operation had been performed for toxic or non toxic goitre The decreasing serum calcium was not due to changes in the serum proteins, as the electrophoretic pattern showed no essential changes

We have no plausible explanation of the fact that while on a normal diet the thyroidectomized patients appeared to have a lower urinary excretion of calcium than the non thyroidectomized persons The increase in serum phosphorus in both groups throughout the experimental periods is presumably due to the supplement of phosphorus and to absorption of phosphorus from the administered sodium phytate

It is a peculiar phenomenon that no definite difference was found in the excretion of phosphorus between the two groups of patients, either in terms of the TRP% or of the phosphate excretion index It might have been expected that the thyroidectomized subjects would show less decrease in TRP% and less increase in PEI than the non-thyroidectomized subjects, but this was not so The explanation may be that stimulation of the parathyroid glands (administration of sodium phytate) might be able to mobilize hormone sufficiently to increase the excretion of phosphorus, but not sufficiently to produce a normal serum calcium level Possibly, more parathormone is required to mobilize calcium from the bones than to increase the urinary excretion of phosphorus

The findings in the patient with manifest parathyroid insufficiency (table II, No 11) are interesting Unlike the other thyroidectomized patients, she showed only a negligible fall in TRP% and no increase in PEI Stimulation of the parathyroid glands could not even increase the excretion of phosphorus

Summary

Serum calcium, serum phosphorus, urinary calcium, tubular re absorption of phosphorus (TRP%), and the phos phate excretion index (PEI) were com pared in 10 non thyroidectomized and 10 thyroidectomized patients, all with normal serum calcium, on (1) normal hospital diet, (2) a low calcium standard diet with a 500 mg supplement of phosphorus and (3) a low calcium standard diet + 500 mg phosphorus + 9 g sodium phytate daily for 4 days

While the non thyroidectomized patients did not exhibit a definite decrease in serum calcium (assessed on the basis of the mean values in each of the 3 experimental periods) the thyroid ectomized patients showed a significant decrease in serum calcium 5 to below the lower normal limit This indicates latent parathyroid insufficiency Yet another patient whose serum calcium level decreased after thyroidectomy, showed a more marked fall Urinary calcium was higher in non thyroide ectomized than in thyroidectomized patients

Throughout the 3 experimental periods the serum phosphorus rose and the TRP% decreased and PΓI increased to approximately the same extent in the two groups of patients In the patient with parathyroid insufficiency, however, there was no change in TRP% or PEI

Presumably, this must be interpreted to the effect that the thyroidectomized subjects frequently cannot produce parathormone enough to maintain the serum calcium level during administra tion of phytate, but sufficient to increase the urinary excretion of phosphorus, determined by the TRP% and PEI Accordingly, a large proportion of patients must be expected to develop latent parathyroid insufficiency after thyroidectomy

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Bacteriuria in Diabetic and Non-diabetic Out-patients

By

RUTH OSTERBY HANSEN

For many years it has been generally assumed that infections occur with increased frequency in diabetics This assumption has also been extended to infections of the urinary tract and has been based on numerous studies concerned with surveys of autopsy materials (2, 3 5 13), as well as with clinical examinations (1, 6, 8, 10)

The criteria adopted in the clinical studies for diagnosing infections of the urinary tract have varied from study to study, and the diagnosis arrived at has often been rather uncertain Similarly, present day research workers are rather inclined to think that the autopsy diagnosis is often made on a too slender basis

It was therefore an unquestionable improvement when bacterial counting on urine was introduced as a method by which to diagnose active infections of the urinary tract Kass (9) contributed greatly by making this method known and widely used

In Kass s material diabetics constituted a separate group Since then, a few additional studies have been published using Kass s method for determining the frequency of infections of the urinary tract in diabetics

Table I shows that the results obtained are rather diverse It is noteworthy that in two of the studies the frequency of infection in diabetics and in non diabetics was found to be the same, the results thus being at variance with those obtained in the studies cited above From comparison of all four studies it must be said that the problem is as yet unsolved

An examination of the bacteriurial frequency in diabetics and non diabetics was therefore carried out at the Århus Kommunehospital during the period February—December 1962 At the same time it was attempted to correlate bacteriuria to diabetic angiopathy and to various characteristics of diabetes

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dilution was determined from direct microscopy of a Gram stained preparation of untreated urine and a moist preparation of the sediment of urine At the latter examination a semi-quantitative method was used since at each examination the same quantity of urine was centrifuged at 2 000 r p m for 5 minutes one drop was distributed under an 18 × 18 mm cover glass and the elements formed were counted in 50 fields (ocular × 10 objective × 40) At all examinations the same microscope was used

In the seeding 0 1 ml was spread with a pipette and 0 01 ml with a standardized platinum loop on to blood agar plates, enriched with yeast extract A series of examinations showed that the spread of the colony counts was the same whether the inoculum was taken by loop or pipetted off

Incubation took place at 35 C for 48 hours in most cases only aerobically and the colonies were counted on plates with colony counts ranging from 50—500

All types of colonies from each specimen were classified in so far as it was deemed relevant Diagnosis of species or genus was made in respect of the Gram negative rods Coagulase test was performed on beta haemolytic staphylococci and the phage type of the positive ones was determined All streptococci were examined with a view to faecal streptococci Beta haemolytic streptococci were classified in accordance with Lancefield s groups

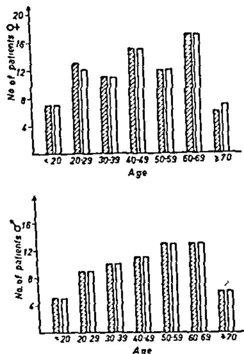


Fig 1 Age and sex incidence of the patients examined (□ = diabetics |///| = non-diabetics)

Results

At bacterial counts of approximately 10^4—10^5/ml it appeared that many colonies were of one definite type clear colonies the size of which varied from barely visible to 1/2—1 mm in diameter At microscopy they were usually found to be small Gram positive coryneiform rods about 1 μ in length It is probable that these bacteria are saphrophytes which are often found in the urethra The following factors lend support to this assumption

1 In the majority of the cultures there was growth of coryneiform rods The number of specimens where there was no dense growth of large colonies, and where the appearance of this colony type could therefore be determined was 139 from women and 127 from men Of these samples, growth of small clear colonies was seen in 117 and 78, respectively

2 Swabs of mucous membrane obtained partly from the area immediately surrounding the urethral orifice partly from immediately inside the orifice, revealed that the 7 women thus examined all had growths of the above colony type

TABLE 1 Four recent investigations on the bacteriurial frequency in diabetic and non-diabetic populations

	No of patients				Bacteriuria (%)			
	Diabetics		Non-diabetics		Diabetics		Non diabetics	
	♀	♂	♀	♂	♀	♂	♀	♂
Kass (9)	54	37	335	102	18	5	6	4
Huvos & Rocha (7)	41	9	41	9	29	–	23	–
Rengarts (12)	46	22	–	–	41	(18)	–	–
O Sullivan et al (11)	92	58	92	58	20	3	19	2

Material

The material consists of 148 diabetics and a control group with the same number of patients, all from the Århus Kommune hospital

The diabetics were chosen from patients attending the diabetes clinic for medical out patients, where the majority of diabetics of the town are controlled This group of patients thus corresponds to a diabetic population However, no children have been included in the material

The control patients were chosen at random from among the remaining medical out patient material without prior knowledge of their diagnosis Patients referred on acount of disorders of the urinary tract or in whom such disorders were subsequently diagnosed, were thus not excluded from the investigation, the total number of such patients was 11 By far the most frequent diagnoses were non inflammatory diseases of the locomotor apparatus

The criteria for inclusion in the control group were 1 No glucosuria 2 Fasting blood sugar level below 120 mg % (determined by Hagedorn Norman Jensen s reduction titration method) Excluded from both groups were patients who were under treatment with antibacterial agents

Both groups consisted of 81 women and 67 men Age and sex incidence are given in fig 1

Methods

All specimens of urine were mid stream-voided samples, collected immediately after careful washing of the area surrounding the urethral orifice During the first half of the period of investigation, the washing was performed with sterile water, and was followed by wiping with sterile dry wads During the latter half of the period the same procedure was adopted, preceded by washing with hexachlorophen 1 ‰ The urine was voided into a sterile glass tube direct whereupon the orifice of the tube was immediately singed The tube was then plugged and placed in a refrigerator within 5—15 minutes

In most cases it was the urine of the second voiding of the day that was collected since in these out patients it was not always possible to obtain the rather more well defined first morning urine

In all cases the author herself assisted by a nurse attempted to obtain the specimen of urine However many patients could not be encouraged to void urine under these circumstances In such cases the patients themselves collected the specimens at the out patient clinic after careful instruction

The specimens were stored in a refrigerator for a few hours prior to seeding

Seeding was then performed using undiluted urine and urine diluted in a series of 10-fold dilutions The required degree of

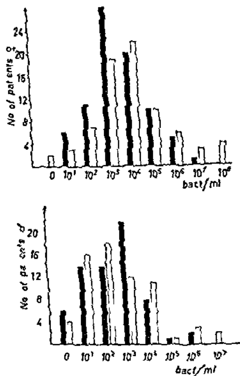


Fig 2 Bacterial counts on urines from diabetics (□) and non-diabetics (■)

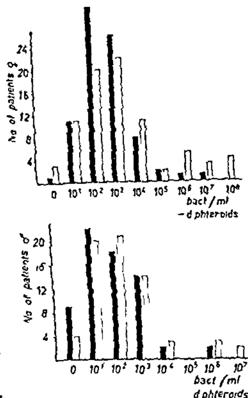


Fig 3 Distribution of the bacterial counts when the coryneform rods are not included (□ = diabetics ■ = non-diabetics)

The age factor

Among diabetic women the frequency of true bacteriuria was slightly increased in patients over 40 years of age but the difference was not significant In respect of men and non diabetic women the figures are too small to be indicative of the possible significance of age

Bacteriuria and the degree of diabetes

Among the women bacteriuria was *more* frequent in the non insulintreated patients The bacteriurial frequency in men was of the same order in both groups

Among the women with a previous history of *coma diabeticum* bacteriuria was more frequent than in the rest of the diabetic women (6 out of 16, as compared with 9 out of 65), whereas 4 of the 5 men with bacteriuria had never had *coma diabeticum*

No connection was found between a high glucose content of the urine specimen examined and bacteriuria

Bacteriuria and the duration of diabetes

The distribution of the patients in diabetes duration groups appears from fig 4

It will be seen that in all men with bacteriuria the duration of diabetes was very long averaging 27 8 years

TABLE II Inc dence of true bacter uria in d a betics and non diabet cs (s gnificant d fference $0\ 001 < P < 0\ 01$ and $0\ 01 < P < 0\ 05$ respect ely)

		No of pat	Pat with bacter ur a (%)
Females	D	81	15 (18 5)
	ND	81	3 (3 7)
Males	D	67	5 (7 5)
	ND	67	2 (3 0)

TABLE III Bacter al find ngs in 25 cases of true bacteriur a

	D	ND
Coli	11	3
Coli + S faecalis	2	
Coli + Sh gella	1	—
Coli + Pr vulgar s	—	1
Alcalescens d spar	1	—
Freund i	1	
Cloaca	1	—
Pro idenc a	1	—
S faecal s	1	—
β l aem s	1	1

3 Urine cultures of 13 catheter specimens from women revealed growth of small coryneiform rods in 7 cases

4 Urine cultures from 3 sections of the same voiding viz the first 5—10 ml the middle part and the last part of the voiding revealed a definite decrease in the colony counts from the first to the third part of the voiding This was shown at three examinations in one woman and three examinations in one man

In the present study small clear colonies exceeding 10^5/ml were found in 22 women and in 1 man If these 23 cases are left out of consideration, the bacterial counts exceeding 10 /ml are attributable in each case to the growth of one or two colony types usually well known urinary pathogenic strains In only one case was there a mixed flora of Gram positive rods and Gram positive cocci at counts of 10^5/ml In 4 cases pure growth of urinary path ogenic strains was found at bacterial counts ranging from 10^4—10^5/ml At this level there often occurred on the other hand growth of mixed contamination flora

Based on these findings true bac teriuria was defined as follows 10^5 or more bacteria/ml of urine when the bacterial count was not attributable to small coryneiform rods or a mixed flora of Gram positive cocci and Gram positive rods

According to this definition true bacteriuria was found in 25 of the 296 patients as shown in table II It will be seen that in the patients examined bacteriuria occurred with greater fre quency in diabetics The results thus support the assumption of an increased frequence of infections of the urinary tract in diabetics

The bacterial findings in these 25 cases are shown in table III It will be seen that in most cases known urinary pathogenic strains usually E coli are involved

Fig 2 shows the distribution of the bacterial counts The frequent occur rence of bacterial counts within the 10^3—10^6 range should be noted In the digrams in fig 3 Gram positive coryne form rods have not been included in the calculation of the bacterial count

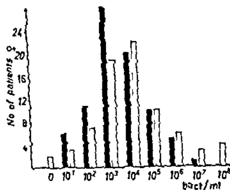


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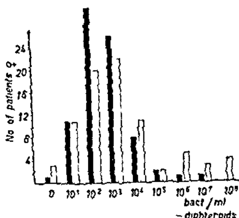


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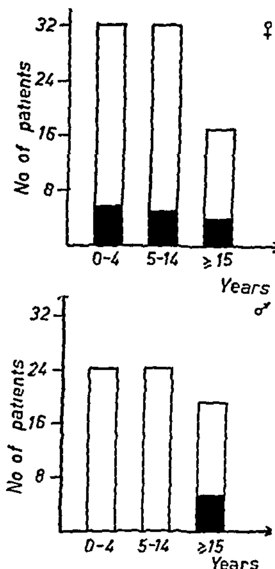


Fig 4 The number of patients with a short medium and long duration of diabetes The duration of diabetes is given in years from the time when laboratory tests gave evidence of the diagnosis The frequency of bacteriuria in the various groups is shown in the diagram (█ = patiens with bacteriuria)

The bacteriurial frequency in women was slightly increased in patients with a duration of diabetes exceeding 15 years (23 5 % against 17 2 %), but the difference is not significant

In the present investigation, bacteriuria in women with a short duration of diabetes (less than 5 years) was found only in patients over 50 years of age It should be pointed out that the duration of diabetes in such patients is not well defined

Bacteriuria and diabetic angiopathy

In the present study, "diabetic renal disease" is defined as findings of proteinuria exceeding 0 5 ‰ at two or more examinations and/or abnormal sediment of urine in respect of erythrocytes and cylinders in diabetic patients The latter criterion was established from the semi quantitative examination of the sediment The limit values used in this connection are more than 50 erythrocytes in 50 fields and more than 5 granular cylinders in 50 fields

The occurrence of diabetic renal disease and its coincidence with bacteriuria will be seen from table IV Four out of 9 men with diabetic renal disease had bacteriuria as compared with 1 out of 58 with no diabetic renal disease In respect of the women the corresponding figures will be seen to be 5 out of 13, as compared with 10 out of 68 The coincidence is thus significant as far as the men are concerned In respect of the women it is in the neighbourhood of the 5 % level

All diabetics except 2 underwent ophthalmoscopy, and the findings were grouped as follows 0 no diabetic retinal changes *Fundus* 1 red dots ("microaneurysms") and possibly phlebopathy *Fundus* 2 haemorrhages and exudates *Fundus* 3 vascular and/or connective tissue proliferations

The ophthalmoscopic findings and the occurrence of bacteriuria were distributed as shown in table V

The bacteriurial frequency in patients with *fundus* 0, 1, 2, and 3 was of the same order in respect of the women All men with bacteriuria had retinal changes corresponding to *fundus* 2

Conditioning factors

The occurrence of factors known or assumed to condition infections of the urinary tract was assessed in the groups of diabetics and non diabetics

Information about urinary calculi, urinary incontinence and difficulties in voiding urine was equally frequent for diabetics and non diabetics

Gynaecological operations and operations on the urinary tract had been performed with equal frequency in diabetics and non diabetics

According to information gained from the patients catheterizations had been performed with equal frequency in the two groups of women Diabetic men were more often catheterized than were non diabetic men

Parturition and abortion were found to have been as frequent in the diabetics as in the control group

The majority of patients (128 men and 126 women) underwent rectal exploration and gynaecological examination performed by the author of the present study Fibromyomas or enlarged uterus were found in 3 diabetic and in 4 non diabetic women None of these had bacteriuria Findings of cystocele as well as of prostatism were classified according to the degree of severity The severest degrees of cystocele (prolapse of the vaginal wall permanently or during abdominal contraction) occurred with a significant increase in frequency in diabetics Among these patients there were however, no cases of bacteriuria Prostatism was slightly more frequent in diabetics than in the patients in the control group but the difference was not significant

Bacteriuria occurred with the same frequency in diabetic women of normal weight and in diabetic obese women (obesity being defined as 110 % or more of the average weights at 30 years of age for men and women according to Hafnia s table of weights) The 3 non diabetic women with bacteriuria were obese In

TABLE IV Correlation between diabetic renal disease and bacteriuria

Bacteriuria		With diabetic renal dis	Without diabetic renal dis
♀	With	[1]5	[1]10
	Without	8	58
		13	68
♂	With	[2]4	[2]1
	Without	5	57
		9	58

[1] P = 0 0[illegible]8
[2] P = 0 00077

TABLE V Correlation between diabetic retinopathy and bacteriuria

		Fundus			
Bacteriuria		0	1	2	3
♀	With	9	2	3	1
	Without	40	4	17	4
		49	6	20	5
♂	With	0	0	5	0
	Without	44	5	12	5
		44	5	17	5

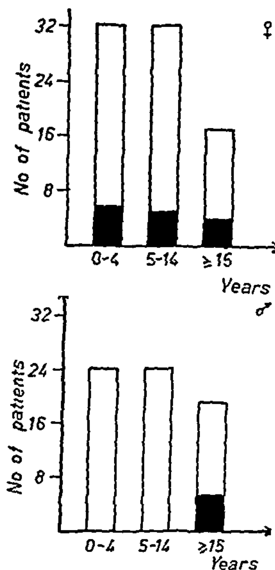


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All diabetics except 2 underwent ophthalmoscopy, and the findings were grouped as follows 0 no diabetic retinal changes *Fundus* 1 red dots ("microaneurysms") and possibly phlebopathy *Fundus* 2 haemorrhages and exudates *Fundus* 3 vascular and/or connective tissue proliferations

The ophthalmoscopic findings and the occurrence of bacteriuria were distributed as shown in table V

The increased frequency of bacteriuria in diabetic women found in the present material was still higher than that found in Kass's material However, Kass's study gives no indication as to age distribution and mode of selection of patients for which reason the results are not comparable

On the other hand the series of patients used in O Sullivan et al's investigation is reasonably comparable with the present material The results obtained by these authors differ decisively from the present findings

The age distribution is different in the two series, O Sullivan et al having a predominance of patients over 60 years of age, whereas the present series has an even age distribution from 20 to over 60 years of age If the difference in results were to be thus explained, the bacteriurial frequency would have to be the same in diabetics and non diabetics over 60 years of age in both materials, whereas the increased frequency for diabetic women in the present material would have to be ascribed to a greatly increased frequency for women between the age of 20—60 This however was not the case

As regards the selection of patients, it would be natural to expect that O Sullivan et al would have found a lower frequency in the patients from the control group since these had been selected from the general population whereas the patients in the control group of the present material were encumbered with various medical diseases

Differences in bacteriological technique might well be an explanation of the dissimilar results obtained Nevertheless, these differences do not seem to be sufficient to explain a difference in the frequency of bacteriuria in diabetics and non diabetics

The evaluation of the plate counts is different in the two studies, O Sullivan et al treating all bacterial counts above 10^5/ml as connoting true bacteriuria Thereby they have included a number of cases which in the present material are termed 'falsely positive', and these cases seem to have been in greater evidence in the control group It should be mentioned that O Sullivan et al find pure growth of E coli in 11 diabetics but only in 6 patients from the control group It is therefore possible that the results of these two investigations are not as dissimilar as would at first appear

Since the number of men with bacteriuria is so small in the present study it would not be justifiable to discuss the coincidence between bacteriuria and other factors as far as the men are concerned

In contradistinction to the results obtained by Huvos and Rocha (7) no increase in the frequency of bacteriuria with increasing age in women could be demonstrated in the present material In this connection it should be borne in mind that the present material consisted of out patients

The increased frequency of bacteriuria in women with a previous history of *coma diabeticum* might conceivably be attributable to the fact that it is particularly risky to use catheterization in patients with acidosis

No certain correlation could be demonstrated between diabetic angiopathy

respect of the men, the low figures showed nothing of interest

Signs and symptoms of infections of the urinary tract

Previous classical case histories of acute pyelonephritis were reported as often for diabetic as for non diabetic women (9 and 11 patients, respectively) But whereas no such patients from the control group had bacteriuria at the time of the investigation, bacteriuria occurred in half the number of diabetics (5 patients)

The number of asymptomatic cases, i e patients with bacteriuria without current symptoms of infection of the urinary tract, was remarkably high, being for diabetics 10 out of 15 women and 5 out of 5 men For the patients in the control group the corresponding figures were 1 out of 3 women and 1 out of 2 men

The connection between pyuria and bacteriuria was not striking The occurrence of pyuria was determined by the semi quantitative examination of the sediment, and for the present purpose it is defined as more than 5 leucocytes per field on the average In respect of the men, all the 7 patients with bacteriuria had also pyuria, whereas the latter was found in 9 out of 15 diabetic women and in 2 out of 3 non diabetic women Pyuria was, however, also frequently found in patients without bacteriuria (among the women 6 diabetics and 7 non diabetics, among the men 1 diabetic and 5 non-diabetics)

Discussion

At the quantitative bacteriological examination of the specimens of urine, the bacterial counts of the present examination were often around 10^3—10^6/ml In many cases the growth consisted of coryneiform Gram-positive rods The distribution curve for the bacterial counts thus differs from the findings of most corresponding studies Coryneiform rods were mentioned only in a few studies on bacterial counts on urine (4, 11) The fact that other research workers do not mention these bacteria may be due to the bacteriological technique used With pour plate cultures these colonies are difficult to discern If the incubation time is reduced to 24 hours, this colony type can only seldom be recognized Furthermore, the substrates used are of decisive importance In the present investigation, blood agar enriched with yeast extract was used Concurrent culture experiments revealed that these bacteria were often better grown on enriched agar than on yeast-free substrate In view of these findings it will appear that there is better agreement with other studies in respect of the distribution of the bacterial counts, if the small coryneiform rods of the present study are not included in the counts (figs 2 and 3)

The frequency of true bacteriuria in the diabetic women of the present material accords with that found by Kass (9) and O Sullivan et al (11) in diabetic female out patients The frequency for male patients, diabetics as well as non diabetics, is similarly of more or less the same order in these three investigations

Rengarts (12) as well as Huvos and Rocha (7) found a higher frequency for diabetic women, but these materials consisted of in-patients

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Primary Myocardial Disease

By

Ole Storstein

Primary myocardial disease has been defined by Mattingly (8) as a cardiac disease, which specifically affects the heart muscle but spares other anatomical structures within the cardiovascular system Of recent years there has been an increasing interest in these condition

The awareness of this disease is partly due to the etiological classification of heart diseases commonly employed during the last 15 years and partly due to hemodynamic studies carried out in obscure cases of heart disease Employing the etiological classification of heart diseases there will be left about $\frac{1}{2}$ per cent of the cases which do not fit into any of the known causes of cardiac disease and which present with signs of myocardial insufficiency of unknown cause Hemodynamic studies of these cases will serve to exclude other structural abnormalities of the cardiovascular system and to demonstrate to what extent the heart muscle is affected

During the last 5 years we have had the opportunity of performing hemodynamic studies in 44 cases of primary myocardial disease In the first part of this paper we are going to present the clinical findings in these patients and in the second part the hemodynamic findings

Part I Clinical studies

Table I shows the age and sex distribution of these patients As will be seen there were twice as many men as women Most of the patients were in the age group of 40—50 years but some cases were seen in early childhood and a few patients were above 60 years of age

As will be seen from table II dyspnea was the most prominent first symptom which was found in one half of the patients One fourth of the patients were discovered accidentally by heart examination They presented either with cardiac enlargement or with a cardiac murmur Chest pain palpitations vomiting and syncope were rare symptoms

The duration of the disease (table III) varied greatly from a couple of months up to 29 years Many of the patients had lived for 10—12 years with known cardiac enlargement or heart murmur when first seen by us

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and bacteriuria There was admittedly a positive correlation with "diabetic renal disease", but too great importance should not be attached to it, since the signs of diabetic renal disease may be signs of chronic pyelonephritis No correlation with retinopathy could be demonstrated However, in order to fully elucidate these problems a larger number of diabetic patients is required

Since factors conditioning infections of the urinary tract occurred with equal frequency in diabetics and patients in the control group, the present material can give no explanation of the increased frequency of bacteriuria found in diabetics

As in other corresponding investigations, the present investigation revealed a number of cases of asymptomatic bacteriuria It could be demonstrated that the presence or absence of pyuria is not a reliable sign for or against the diagnosis of bacteriuria These factors, as well as the rather high frequency of bacteriuria, indicate that bacterial counts on urine should be more extensively used as a bacteriological routine examination There is a particular indication for using the method when the usual bacteriological examination gives results which are difficult to interpret However, the quantitative aspect should not be over-emphasized at the expense of the qualitative

Summary

Bacterial counts were performed on mid stream voided urines from 148 diabetic out patients, 81 women and 67 men, and from a similar number of control patients

The definition of true bacteriuria used in the present study takes account of the qualitative as well as the quantitative aspect

The frequency of true bacteriuria was found to be significantly increased in diabetics as compared with patients from the control group, being for women 18 5 % and 3 7 %, respectively, and for men 7 5 % and 3 0 %, respectively

No correlation was found between the duration of diabetes and the frequency of bacteriuria in women, whereas all 5 men with bacteriuria had a duration of diabetes exceeding 15 years

No connection between late diabetic vascular disorders and bacteriuria could be demonstrated in the present material

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Steell variety From earlier studies of this condition it is known that a diastolic gallop sound is a common finding either a third heart sound indicating a dilated left ventricle or a fourth heart sound (atrial gallop) In our material a gallop sound was found in 11 patients

The electrocardiogram table VI was normal in 7 patients Three patients had atrio-ventricular conduction disturbances and 4 patients presented with auricular fibrillation Signs of left ventricular strain was the most common electrocardiographic finding while right ventricular strain was found more seldom This electrocardiographic picture supports the hemodynamic observations to be mentioned later Three patients presented with an electrocardiogram indicative of myocardial infarction. Two of these patients had endocardial fibroelastosis and their electrocardiogram indicated anterior myocardial infarction This was due to anomalous origin of the left coronary artery from the pulmonary artery The third patient with electrocardiographic signs of myocardial infarction was a patient with progressive muscular dystrophy

X ray of the heart (table VII) was normal in only 5 patients The most common finding was enlargement of the left ventricle In some patients there was also enlargement of the right ventricle and left atrium On progression of the disease pulmonary congestion appeared

Fig 1 presents the frontal X ray of a 15 year-old boy where cardiac enlargement was discovered on routine clinical examination There is a pronounced cardiac enlargement mainly of the left ventricle but also slight enlargement of the right ventricle in this boy who had no symptoms

Table VIII presents the diagnosis from clinical and hemodynamic studies in these patients As we see there were 22 patients with myocardial disease of unknown cause also called idiopathic myocardial disease (12) These cases are either chronic myocarditis or myocardial fibrosis or hypertrophy of unknown cause There were 4 patients with progressive muscular dystrophy a disease

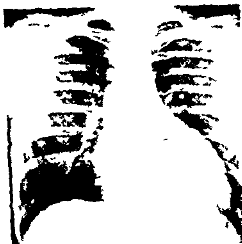


Fig 1 X ray of the heart of a 15 year old boy showing predominantly enlargement of the left ventricle

which is known to affect the heart in many of the patients Four patients had scleroderma with myocardial involvement Three patients had primary amyloidosis One of these was studied by autopsy and 2 confirmed from biopsy One patient had Boeck s sarcoid Two children had a peculiar disease with pronounced muscular hypertrophy also of the heart muscle (13) Four children had endocardial fibroelastosis 2 of these were secondary to anomalous origin of the left coronary artery from the pulmonary artery We saw 1 patient with beri beri of the wet type Finally there were 3 patients with muscular subaortic stenosis This disease which first was described by Brock (3) affects the intraventricular septum and produces a subaortic stenosis and sometimes also a subvalvular pulmonic stenosis As is well known from other studies the stenosis is partly functional and varies with exertion and is affected by drugs It is made worse by digitalis Two of our patients also had pulmonic subvalvular stenosis This condition will be discussed in more detail in the hemodynamic part of this paper

The prognosis in these patients is rather grave as 9 of our patients died during the observation period ranging from a few months up to 5 years

TABLE I Age and sex

Years	Men	Women	Total
0–10	7	1	8
11–20	3	3	6
21–30	2	5	7
31–40	3	0	3
41–50	7	4	11
51–60	4	1	5
61–70	3	1	4
Total	29	15	44

TABLE II First symptom or sign

Dyspnea	22
Heart enlargement	7
Heart murmur	5
Chest pain	2
Palpitations	3
Vomiting	1
Syncope	1

TABLE III Duration of illness (year)

<1	17
1–5	11
6–10	7
11–29	6
Unknown	3
Total	44

TABLE IV Symptoms

Dyspnea	33
Edema	18
Cardiac pain	6
Palpitations	14
Syncope	1
Cyanosis	1
Congestive heart failure	20

TABLE V Heart murmurs

Systolic murmur (grade 2)	18
Systolic murmur (grade 3)	14
Systolic murmur (grade 4)	2
No murmur	10
Diastolic murmur	2
3 Heart sound	7
4 Heart sound	4

TABLE VI Electrocardiogram

Normal	7
Conduction disturbances	3
Auricular fibrillation	4
Left ventricular strain	24
Right ventricular strain	7
Myocardial infarction	3

TABLE VII X ray of the heart

Normal	5
Left ventricular enlargement	13
Right ventricular enlargement	6
Left and right enlargement	20

On admission dyspnea was the most prominent symptom, found in 33 of the patients (table IV) Edema was found in 18 patients and palpitations in 14 Almost one half of the patients presented with congestive heart failure on admission It is to be noted that cardiac pain was seldom found in this patient group

On cardiac examination (table V) a systolic murmur was found in 34 of the patients The systolic murmur was usually of moderate intensity grade 2—3 It was strongest at the apex or at the lower left sternal border It was usually of ejection type In some cases a holosystolic murmur was found, indicating mitral or tricuspid insufficiency A diastolic murmur was found in only 2 patients It was of the Graham

TABLE IX Hemodynamics in patients with myocardial disease with *normal* PCV — pressures

Age	Sex	Art O_2-satur	Cardiac index	Pulmonary artery pressure (mm Hg)	Pulmonary capillary venous pressure (mm Hg)	Right atrial mean pressure (mm Hg)	Pulmonary arteriolar resistance dynes/sec/cm ^{5}
Group A Normal cardiac output							
43	♂	98	3 8	18/5	—	2	—
58	♂	98 6	3 0	40/15	5	0	315
17	♀	96	3 4	17/6	5	0	70
10	o	97	4 9	17/9	5	3	160
3	o	99	5 0	29/13	5	0	320
2	♂	93	3 6	19/8	7	1	140
/	♂	—	4 3	19/14	0	−1	500
2	♂	98	6 4	42/12	6	0	265
63	♂	92	3 0	36/8	—	3	—
Mean		96	4 2	26/10	4	1	240
Group B Low cardiac output							
38	♂	90 3	2 5	18/5	5	0	40
67	♀	97 2	1 5	24/8	5	−2	190
29	♀	95	2 7	18/10	8	4	80
49	♀	95	2 3	35/12	—	4 5	—
52	♀	90 7	4 2	32/10	3	0	365
61	♂	91	2 6	21/8	3	1	167
36	♂	95	2 7	18/4	5	0	80
23	♀	95	2 2	12/5	5	2	67
Mean		94	2 4	22/8	5	1	141

myocardium is impossible to say Virological studies carried out in earlier reports have all been negative (12), and biochemical studies have so far failed to throw any light on the etiology of this disease Studies of myocardial metabolism carried out by Wendt et al (15) have shown increased myocardial oxygen extraction with reduced cardiac output and a negative myocardial balance of pyruvate and lactate Glycolysis has also been demonstrated in the hearts of these patients and greater activity of malic acid dehydrogenase and aldolase in coronary venous than in arterial blood, suggesting increased permeability of the myocardial cell The same pattern was found in all types of myocardiopathies studied by Wendt et al (15), who concluded that metabolic studies failed to reveal a distinct metabolic pattern which might help to differentiate various etiological groups of myocardial disease

The familial occurrence of primary myocardial disease has been noted earlier (5) In our group of patient

TABLE VIII Clinical diagnosis

Catheterization diagnosis		Clinical diagnosis: Verified	Congenit	Mitral insuff	Arteriosclerotic heart disease	Verified by autopsy or biopsy
Myocardial disease	22	15	4	3	–	4
Progressive muscular dystrophy	4	4	–	–	–	3
Scleroderma	4	4	–	–	–	4
Amyloidosis	3	2	–	–	1	3
Sarcoidosis	1	1	–	–	–	1
Muscular hypertrophy	2	2	–	–	–	–
Fibroelastosis	4	4	–	–	–	2
Beri beri	1	1	–	–	–	–
Subaortic stenosis	3	3	–	–	–	–
Total	44					17

Of the patients who died 7 were in hemodynamic groups 2A and 2B (table X), presenting the hemodynamic findings of the patients most severely affected Two patients died however who at the time of the study were in hemodynamic group 1A, but the illness progressed rapidly and led to death in a couple of years

Pathological studies will show myocardial involvement to a varying extent The picture presented in fig 2 is from a patient who died with a refractory cardiac failure As will be seen there is marked increase in connective tissue and replacement of myocardium by fibrous tissue The myocardial fibers which are left, are hypertrophied There are no signs of myocardial inflammation From the pathologico-anatomical picture it is difficult to say if this is *the reciduum of an old myocarditis or if it is a primary myocardial hypertrophy or fibrosis*

Two features, which have been mentioned in earlier reports on this condition were absent in our series

1 There was only one patient with a history of excessive alcoholic intake This is to be compared with Dye et al s report (4) of 21 alcoholics in a group of 32 patients with primary myocardial disease and Sanders (12) *15 of 27 patients with idiopathic myocardial* disease

2 *Embolic episodes were not noted in our* series neither in the clinical study nor at autopsy Embolism has been a feature of many earlier studies of this condition Dye et al (4) 13 embolic episodes in 32 patients Spodick and Littmann (14) 36 in 72 patients mostly due to mural thrombosis Brigden (2) 20 instances of mural thrombosis in 32 necropsies Fowler et al (6) 10 in 18 necropsies

Discussion

The etiology of the cardiac disorder has been clarified in 19 patients in our series where the cardiac affection is a part of a systemic disease In the other 25 patients the etiology is obscure Pathological studies in these cases will usually show the picture demonstrated in fig 2 with *a diffuse myocardial fibrosis If this is a* chronic myocarditis of unknown etiology or if it is a primary fibrosis of the

graphic picture found in arteriosclerotic cardiac disease The patient where a diagnosis of arteriosclerotic heart dis ease was made was a patient with *primary amyloidosis* His electrocardio gram showed diffuse ST T changes (fig 3), and hypoxemia test showed ag gravation of ST depression apparently confirming the diagnosis of angina pectoris His cardiac pains showed typical relation to exertion but were atypical as they were relieved by nitroglycerin only after 10—15 minutes An electrocardiogram taken shortly before death showed low voltage in extremity leads and diffuse myocardial involvement in unipolar leads (fig 3) On autopsy the coronary vessels were patent There was diffuse infiltration by *amyloid in the heart* muscle which was gray red and very firm unyielding to pressure It is readily understandable that such a myocardium may demonstrate a constrictive myocar ditis a differential diagnosis to be dis cussed later on

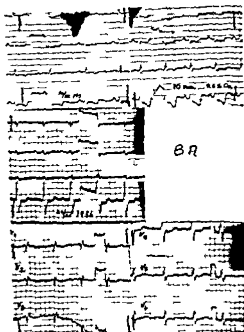


Fig 3 Electrocardiogram from a patient with *primary amyloidosis of the heart* demonstrating slight S—T depression with positive hypoxemia test and diffuse myocardial involvement

The possibility that primary myocardial disease may be an autoimmune disease has been discussed, but so far there are no studies to support this interesting theory

Part II Hemodynamic studies

Hemodynamic studies have been carried out in all our 44 patients Cardiac output and intravascular pressures were only studied at rest The findings are presented in tables IX and X These studies showed varying degrees of myocardial involvement and we have grouped the patients according to the hemodynamic findings irrespective of etiology As will be seen in group 1 we included patients with normal pulmonary capillar venous (PCV) pressure and in group 2 those with *elevated PCV pressures These two groups* were again divided into subgroups A and B group A with normal cardiac output and group B with reduced cardiac output

In group 1 A there were 4 patients with essentially normal hemodynamic findings while the other 5 patients had slightly elevated pressures in the pulmonary artery and elevated pulmonary arteriolar resistance Of the 7 patients in group 1 B who all had a low cardiac output 4 patients had normal pressures in the pulmonary circulation whilst 3 patients had slightly elevated pressures The patients in group 2 all had elevated PCV pressures and all *of them except 1 in group* 2 A had elevated pulmonary artery pressure In group 2 A 8 patients had normal pul monary arteriolar resistance while 5 patients had elevated resistance up to 830 dynes In group 2 B the pressures in the pulmonary circulation were of about the same magnitude



Fig 2 Myocardium showing increase in connective tissue and replacement of myocardium by fibrous tissue Hypertrophy of myocardial fibres Hematoxylin eosin × 100

there were two brothers 30 and 35 years of age Their father died at the age of 68 years of heart disease Three other brothers were dead, respectively 5, 23 and 35 years old These 2 patients are the only representatives of familial cardiopathy in our series

The clinical course of this condition varies greatly There are patients with known cardiac disease of up to 29 years with only slight cardiac affection while in other cases cardiac failure starts early, apparently only after a few months Usually these patients respond initially to treatment with improvement and with regression of cardiac enlargement The episodes of cardiac failure return however and ultimately refractory cardiac failure develops The treatment in our patients has been carried out along the usual lines with digitalis and dehydration, bed rest and theophylline preparations as indicated

We should like to stress the importance of respiratory infections in this condition As far as we can see, this has not been mentioned in earlier reports Characteristically respiratory infection sometimes makes the disease manifest and it always leads to an aggravation of heart failure It is conceivable that respiratory infection will tend to add an increased burden on an already heavily taxed myocardium, partly by the increased metabolic demand placed on the heart by the fever and partly by lung involvement with anoxia and increased pulmonary vascular resistance

The diagnostic problems in our cases are illustrated by table VIII Four patients were thought to have congenital heart disease from the clinical examination The suspicion was raised because of a cardiac murmur and enlargement of the heart on X-ray The diagnoses entertained were ventricular or atrial septal defect A diagnosis of mitral and/or tricuspid insufficiency was made in 3 patients This is not surprising as dilatation of the cardiac chambers will produce a relative insufficiency of the atrio-ventricular valves and the phonocardiogram will demonstrate a holosystolic murmur It is important to have the possibility of primary myocardial disease in mind when one makes a diagnosis of mitral or tricuspid insufficiency in these days when surgical treatment of mitral insufficiency is a possibility It is surprising that the diagnosis of arteriosclerotic heart disease was only made once in our series One should think that a diffuse arteriosclerosis of coronary vessels would present with a picture of diffuse myocardial fibrosis with myocardial insufficiency We think that the reason why this diagnosis is so seldom made in primary myocardial disease is the specific electrocardio

graphic picture found in arteriosclerotic cardiac disease The patient where a diagnosis of arteriosclerotic heart disease was made was a patient with primary amyloidosis His electrocardiogram showed diffuse ST T changes (fig 3) and hypoxemia test showed aggravation of ST depression apparently confirming the diagnosis of angina pectoris His cardiac pains showed typical relation to exertion but were atypical as they were relieved by nitroglycerin only after 10—15 minutes An electrocardiogram taken shortly before death showed low voltage in extremity leads and diffuse myocardial involvement in unipolar leads (fig 3) On autopsy the coronary vessels were patent There was diffuse infiltration by amyloid in the heart muscle which was gray red and very firm, unyielding to pressure It is readily understandable that such a myocardium may demon trate a constrictive myocarditis a differential diagnosis to be discussed later on

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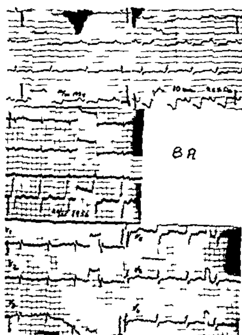


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TABLE X Hemodynamics in patients with myocardial disease with elevated PCV — pressures

Age	Sex	Art O_2 satur	Cardiac index	Pulmonary artery pressure (mm Hg)	Pulmonary capillary venous pressure (mm Hg)	Right atrial mean pressure (mm Hg)	Pulmonary arteriolar resistance dynes/sec/cm⁻⁵
Group A Normal cardiac output							
25	♀	97	3 0	43/18	16	12	240
10	♀	98	4 9	22/6	9	6	75
42	♀	96	4 5	58/26	16	8	236
15	♂	94	3 4	30/13	12	3	133
24	♀	100	3 3	87/38	29	4	372
15	♂	96	4 4	35/12	14	8	131
42	♂	94	3 2	52/19	21	8	133
39	♂	90 9	3 7	38/16	16	6	110
30	♂	92	5 0	37/17	16	2	82
17	♀	90	4 0	46/31	26	5	255
19	♀	99	4 4	17/7	11	2	35
1½	♂	99	4 3	42/28	16	4	890
5	♂	97	5 3	35/25	18	2	151
44	♂	94	3 0	38/13	14	6	135
Mean		98	4 1	42/19	16	5 5	213
Group B Low cardiac output							
46	♂	94	2 6	55/30	25	6	300
44	♀	87	1 9	47/20	28	13	138
44	♀	94	2 0	46/15	19	1 5	193
65	♂	89	2 9	48/29	26	7	182
43	♂	96	2 5	73/35	37	9	196
75	♂	89 5	1 8	43/10	—	10	—
51	♂	97 7	1 6	33/20	19	8	280
44	♂	97	1 7	23/14	13	7	125
52	♂	91	1 6	50/18	21	0	260
59	♀	96	2 0	32/9	15	7	172
Mean		93	2 1	45/20	22	7	205

as in group 2 A but here the cardiac output was reduced The pulmonary arteriolar *resistance* was slightly elevated in 6 of these 10 patients It is to be noted that the pulmonary hypertension in these patients usually was of only moderate severity, the highest pressures *being* 87/38 It is further to be noted that there were no patients with increased pressure in the right atrium and normal pressure in the pulmonary capillaries and that some patients had normal pressure in the right atrium despite heavily increased pulmonary capillary venous pressure This finding demonstrates that the left ventricle is earlier and more heavily affected than the right ventricle in primary myo-

cardial disease and it confirms the findings made by electrocardiographic studies mentioned in part one of predominant left ventricular strain in this condition

Arterial oxygen saturation was normal in the first 3 subgroups Only in 3 patients in the most severely affected group 2 B was there a slight reduction in arterial oxygen saturation a finding which is usually made in patients with lung congestion due to severe heart failure

This study shows that the heart may be affected in two ways by primary myocardial disease

1 By back pressure due to a failing myocardium as illustrated by elevated pressures in the left and later in the right atrium and

2 By a reduction in cardiac output due to a forward failure as the function of the heart as a pump is compromised This finding illustrates that both theories put forward to explain heart failure hold true The heart may partly fail by a back pressure effect and partly by a forward failure effect

As will be seen there is no uniform pattern of the hemodynamic findings in this condition Only in advanced cases with frank congestive failure is the hemodynamic picture uniform as demonstrated by the patients in group 2 B Only these patients fulfill the criteria set up by Mattingly (8) Low cardiac output increased arteriovenous oxygen difference elevated pressures throughout the pulmonary circulation and in the later stages elevated pressure also in the right atrium The importance of carrying out hemodynamic studies in these patients is first and foremost from the viewpoint of differential diagnosis to exclude congenital and valvular heart disease

There are 2 specific conditions in this disease group which may be elucidated by hemodynamic studies constrictive myocarditis and muscular subvalvular aortic stenosis

The term *constrictive myocarditis* has been applied to cases of primary myocardial disease with severe fibrosis of the myocardium or infiltration of the myocardium by foreign material rendering it stiff and unyielding result ng in an ineffective diastolic relaxation

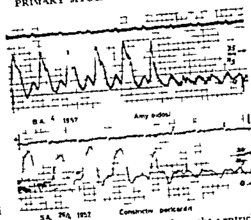


Fig 4 Pressure curves from the right ventricle and right atrium in a patient with cardiac amyloidosis compared with pressure curves in a case of constrictive pericarditis

of the myocardium In this instance the myocardial disease behaves like a constrictive pericarditis which is characterised by increased diastolic pressure in the right and left ventricle and accordingly elevated pressures in the right and left atrium with systemic and pulmonary congestion In constrictive pericarditis there is a characteristic pressure curve from the right ventricle with an early diastolic dip and a late diastolic plateau The same pressure pattern is found in cases of constrictive myocarditis (11) As will be seen from fig 4 the pressure pattern in constrictive pericarditis and constrictive myocarditis may be very similar Nye et al (10) maintain that the diastolic plateau is higher in constrictive pericarditis than in myocarditis In the first condition it should be more than 1 3 of the pulse pressure in the right ventricle As will be seen from fig 4 this is no uniform finding

The differential diagnosis between constrictive pericarditis and constrictive myocarditis is very important in those cases where there are no pericardial calcifications on X ray In both instances there is congestive heart failure often with considerable liver enlargement and severe venous congestion in the neck. Usually there are no murmurs to be heard In both conditions there may be a protodiastolic third heart sound in constrictive pericarditis a pericardial clique and in

TABLE XI Pressures in right and left heart in muscular septal hypertrophy

Age	Sex	Date	Aorta	Sub valv	Left ventr	Pulm art	Infundibul	Right ventr
14	♂	10/12/63	–	–	–	28/12	30/2	67/2
		20/1/64	93/54	86/14	160/14	57/30	–	31/5
		24/2/64	–	–	–	25/0	25/0	60/0
		24/2/64[1]	–	–	–	32/0	–	32/0
19	♂	10/5/61	80/60	80/60	170/0	–	–	–
		6/9/63	–	–	–	26/10	–	41/0
43	♂	25/10/63	85/60	100/10	135/10	–	–	–

[1] After operation

constrictive myocarditis a diastolic ventricular filling sound. The heart is quiet in both conditions. There are small pulsations on X-ray and there is a moderate cardiac enlargement. One should expect the heart to be more enlarged in myocarditis than in pericarditis but this is not a reliable sign.

The absence of pericardial effusion may be demonstrated in 3 ways. 1) On cardiac catheterization, the cardiac catheter may reach the right cardiac border without any interposing layer of fluid between the catheter and the cardiac border. 2) By angiocardiography, and 3) by injection of 50 % carbon dioxide gas.

The hemodynamic studies show very much the same findings and the differential diagnosis is an enigma. In our experience the most reliable finding on hemodynamic examination is an equal elevation of the pressure in the right and left atrium in cases of constrictive pericarditis. As demonstrated by our study, the pressures are always higher in the left than in the right atrium in primary myocardial disease. In some cases one has to perform a thoracotomy to clarify the diagnosis as was done in 2 patients in Dye et al.'s (4) series. Where constrictive pericarditis is found a pericardial decortication may be carried out. If no constrictive pericarditis is found, a myocardial biopsy is done.

Muscular subvalvular aortic stenosis

As mentioned in the clinical part we have seen 3 patients with this disease and their hemodynamic findings are illustrated in table XI. Catheterization of the left ventricle and aorta has been carried out in all 3 patients and in 2 patients a right heart catheterization has also been done. There is a characteristic pressure pattern in this condition as demonstrated in fig. 5, a low pressure in the aorta, in the subvalvular chamber the systolic pressure is of the same magnitude as the systolic pressure in the aorta and the diastolic pressure is of the same height as the diastolic pressure in the left ventricle, in the left ventricle there is a high systolic pressure (1). In this interesting condition there is a muscular hypertrophy of the interventricular septum, producing a subvalvular stenosis on the left and sometimes also on the right side. The stenosis is partly functional. It may disappear following sympatholytic drugs and it is made worse by digitalis (7). In one of our patients, as will be seen from table XI the

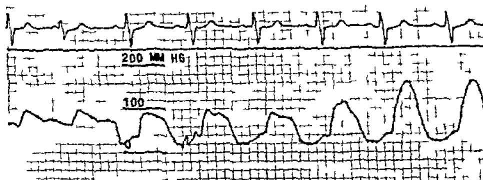


Fig 5 Pressure curve recorded during withdrawal of the catheter from the aorta to the left ventricle in a patient with muscular subvalvular aortic stenosis



Fig 6 Angiocardiogram showing the conical narrowing of the subvalvular chamber of the left ventricle during systole



Fig 7 Angiocardiogram showing diastolic relaxation of the subvalvular chamber

gradient on the right side of the heart was absent on one occasion when during catheterization of the left ventricle the catheter inadvertently entered the right ventricle

There is a characteristic angiocardiographic picture in subvalvular aortic stenosis as demonstrated in figs 6 and 7 In systole (fig 6) there is conical narrowing of the subvalvular chamber while in diastole (fig 7) the chamber dilates apparently normally Similar observation has been made by Braunwald et al (1)

The surgical treatment of this condition has been under discussion in later years We feel that the proposal of Morrow and Brockenbrough (9) should

be followed Carrying out an incision of the ventricular septum from the left side and if needed also on the right side of the heart This operative procedure has been carried out in one of our patients, apparently with good result

Summary

Clinical and hemodynamic studies have been carried out in 44 patients with various forms of diseases primarily affecting the myocardium There were twice as many men as women and most of the patients were below 50 years of age Dyspnea was the most common symptom but sometimes the heart disease was discovered accidentally The duration of the disease varied greatly from a few months up to 29 years Almost half of the patients were in congestive heart failure when first seen A systolic murmur of moderate degree was found in most of the patients A gallop sound was found in one fourth of the patients Both the electrocardiogram and the X-ray showed predominantly involvement of the left ventricle in this condition The diagnosis is usually made on clinical grounds Septal defects and mitral- or tricuspid insufficiency are the main points to be considered in the differential diagnosis

The hemodynamic picture is partly dominated by reduction in cardiac output and partly by elevated filling pressure of the heart, first and foremost on the left side A few of the patients present with a picture of constrictive myocarditis which closely simulates constrictive pericarditis The differential diagnosis between these two conditions may be difficult The main point in our experience is an equal elevation of the pressure in both atria in constrictive pericarditis, while in constrictive myocarditis the pressure is most elevated in the left atrium

Muscular subaortic stenosis may be suspected on clinical grounds Hemodynamic studies reveal a characteristic pressure curve and a characteristic angiographic picture In two of the three cases seen, there was stenosis also on the right side of the septum

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Blood Histamine and Basophil Leukocytes in Polycythemia

By

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In polycythemia the number of basophilic leukocytes (1, 3 6 9, 14) and the histamine content (4, 5) of the circulating blood are increased Though this has long been known, it would appear that these changes have never been systematically studied for their value as criteria in the classification of polycythemia This paper is concerned with basophil leukocytes and histamine in the blood of untreated and ^{32}P treated cases of polycythemia vera, and secondary polycythemia due to hypoxia Special attention is paid to 3 cases of polycythemia in which leukemia developed

Material

The material consisted of 64 patients (33 men 31 women) with polycythemia treated at the department of radiotherapy Lund and followed up for one year Only patients with a hematocrit of more than 54 %, were accepted (11) Examinations of the patients included blood gas analysis and determination of the plasma volume In 4 of the patients the pO_2 was below 90 mm Hg, and in these polycythemia was classified as secondary

Fifteen of the patients with polycythemia vera had not received any treatment before the time of the first examination Forty three had been treated previously or were treated during the time of the investigation with ^{32}P and then orally in a dose of about 0 1 mCi/kg body weight Most of these patients were followed up at 3 month intervals A 50 year-old woman (E P table II) was treated with repeated phlebotomy In the course of about 6 months all together 2,500 ml of blood was tapped One patient (O E) was examined 1 month after phlebotomy

Acute leukemia developed in 2 of the patients One of them a 76 year-old woman with 8 years history of polycythemia vera had received all together 50 mCi ^{32}P which was the largest total dose given in the present material Two years after the end of treatment pancytopenia and acute leukemia developed The number of basophils and the blood histamine level were then normal The patient died two months later with terminal leukocytosis and basophilia The findings at necropsy confirmed the diagnosis of acute leukemia The other patient was a

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TABLE I

		Normals	Patients with polycythemia vera: Untreated	Patients with polycythemia vera: Treated with ^{32}P	Secondary
No. of cases		90	15	43	4
Basophil leukocytes/mm³	Mean	44	[1]124	110	—
	Range	8—122	55—225	10—1 07?	—
Histamine µg/100 ml blood	Mean	7 5	19 0	14 1	6 2
	Range	2 5—11 8	10 3—28 ?	2 9—9? 5	?7—9 6

[1] Mean value of 11 untreated cases

TABLE II Cases of untreated polycythemia vera

Cases	WBC (per mm³)	Basophil leukocytes (per mm³)	Histamine µg/100 ml blood
V O	5 000	105	28 2
H T	8 800	150	27 5
H P	7 100	114	24 2
E N	4 700	94	16 4
L N	7 300	73	15 4
I N	19 700	158	13 5
G N	7 ?00	122	12 8
H J	5 300	95	15 3
M M	5 000	65	10 3
E E	9 600	—	?2 3
L I	7 700	—	13 5
A J	7 500	105	25 8
S J	4 800	89	21 6
L P	5 300	—	15 9
S S	11 700	225	?2 5
S S	10 800	—	24 8
E P	7 500	—	?3 5
E P[1]	9 100	?09	3? 7
E P[2]	7 500	—	43 8
O E[3]	7 200	7?	18 5

[1] 7 months after first determination

[2] 7 months after first determination (after phlebotomy)

[3] 10 months after first determination

[4] 1 month after phlebotomy

62 year-old man with 19 years history of polycythemia He received all together 39 mCi ^{32}P During the last 6 months the blood values fell markedly The number of myeloblasts in the blood was 20 % and sternal puncture showed myeloblastic proliferation The blood histamine and the number of basophilic leukocytes were normal at the last follow up examination

Chronic myeloid leukemia was suspected in one case The patient was a 54-year-old woman Polycythemia had been diagnosed 8 years previously She received all together 34 mCi ^{32}P Two years before the present examination the number of leukocytes rose to 110 000/mm³ Sternal puncture suggested the diagnosis of chronic myeloid leukemia and the patient was treated for some months with a small dose of Myleran The number of white blood cells fell to 15 000 mm³ during treatment The number persisted at this level for some months after withdrawal of the drug and then began to rise again and at last follow up it was 70 000/mm³ Differential count 3 % metamyelocytes 5 % myelocytes and 1 % promyelocytes The serum vitamin B_{12} was increased (1 800 pg ml The alkaline phosphatase score was high Blood histamine 93 µg/100 ml Analysis of the phagocytic activity of the leukocytes by the method of Brandt (? showed a distribution of the type seen in chronic myeloid leukemia

TABLE III Cases of polycythemia vera treated with ^{32}P

Cases	Time after single oral dose of ^{32}P (months)	Hb (g/100 ml)	WBC (per mm³)	Basophil leukocytes (per mm³)	Histamine µg/100 ml blood
H P	0	22 9	7 100	114	24 2
	3	18 6	5 400	38	7 5
	6	12 9	5 700	—	7 8
A O	0	19 1	5 000	105	28 2
	3	16 3	5 000	85	16 3
M M	0	19 1	5 000	65	10 3
	3	12 0	5 000	55	4 2
U H	0	18 7	8 600	353	56 3
	3	14 5	9 100	191	9 0
E S	0	17 5	18 800	225	33 0
	3	11 7	6 100	37	5 6
	6	13 0	9 800	59	11 8
	9	15 0	11 200	—	20 0
A L	0	17 3	5 200	57	8 3
	3	12 7	3 200	10	5 1
	6	11 4	3 400	14	3 8

Methods

The *blood histamine* was determined with a fluorometric method described by Shore et al (15) By recrystallization of orthophthaldialdehydes in heptane low blank values were obtained Blood samples were collected in tubes with Versene and diaminoguanidine An Aminco-Bowman spectrophoto-fluorometer was used for the measurements The mean histamine content per 100 ml of blood from 90 registered blood donors was found to be 7 5 µg (range 2 5– 11 8)

The number of *basophil leukocytes* in the blood was determined with an indirect method (12) using blood smears stained according to Undritz (17) As a rule 1 000 cells were counted

Results

The concentration of histamine and the numbers of basophil leukocytes found are summarized in table I The cases of polycythemia vera not treated with radioactive phosphorus are presented in table II In 14 of the cases the blood histamine and the number of basophil leukocytes were determined simultaneously In 3 patients basophils were not counted

In one patient (E P) the blood histamine at the first examination was found to be clearly increased 23 5 µg/100 ml After repeated phlebotomy the histamine content increased and at follow up 7 months after the first examination the number of basophil leukocytes was also increased At the following examination 3 months later the values were still higher but the hemoglobin level was no longer elevated

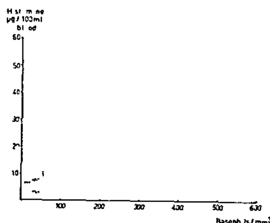


Fig 1 Correlation between blood histamine and basophil leukocytes in cases of polycythemia vera

and the serum iron was decreased In another patient (O E) with normal hemoglobin level 1 month after phlebotomy the blood histamine was increased

Table III gives values for the patients treated orally with a single dose of ³²P Examination 3 months later invariably *showed the number of basophil leukocytes* and the histamine content of the blood as well as the hemoglobin had decreased In a patient followed for 9 months after the dose of ³²P the histamine had increased already after 6 months and still more after 9 months In two patients followed for 6 months the histamine had not significantly changed after the initial decrease

The remaining patients treated with ³²P (table I) did not receive *any further* dose of ³²P during the period covered by *the present* investigation As expected, the values found in these patients differed, the blood histamine and the number of basophil leukocytes varied with the phase of the disease and the interval after the last treatment with ³²P

Fig 1 shows the correlation between the blood histamine content and the number of basophil leukocytes per mm³ blood in patients with polycythemia vera The extremely high value, 93 µg histamine/100 ml blood corresponding to 1072 basophils/mm³, is not included in the figure Apart from this, the figure includes all histamine-basophil determinations made in the untreated and treated cases of polycythemia vera Most of the *patients are represented twice or more* in the figure The correlation coefficient between the number of basophil leukocytes and the blood histamine in the entire series of patients with polycythemia vera was 0 91

Discussion

It is clear from table II that the histamine content of the blood was abnormally *high in 16 of 17 cases of polycythemia* vera not treated with ³²P In most of *these patients the histamine* was clearly increased despite a normal total number of leukocytes in the blood Valentine et al (18) found that cases of untreated polycythemia vera with 'no or minimal leukocyte abnormalities have shown no or slight deviation from normal' In none of our patients with secondary polycythemia was the blood histamine *increased The findings suggest that* measurement of the blood histamine might be useful for distinguishing un treated cases of polycythemia vera from secondary polycythemia

As expected (4, 5) a close correlation was found between the number of basophil leukocytes and the *blood histamine* content In our material the

correlation coefficient was 0 91 The mean error of the basophil leukocyte count by the indirect method used is large when the number of basophil is low Here determination of the blood histamine content gives more exact information

It is established that polycythemia vera can develop in leukemia (10, 13) The frequency of leukemia is higher among patients treated with ^{32}P (8, 13 16) But treatment with radioactive phosphorus prolongs survival (7, 19) and may thereby increase the risk of leukemia The leukemia in ^{32}P treated patients is usually of the acute type (16) and this wa observed in 2 of our cases The blood histamine content was normal in these patients at the time of diagnosis of leukemia In the first case terminal leukocytosis and basophilia occurred, which is remarkable in acute leukemia Unfortunately the blood histamine was not determined in this stage of the disea e This case of polycythemia vera with supervening leukemia suggests that the acute leukemia in patients with polycythemia differs from ordinary acute leukemia

In one of our cases incipient chronic myeloid leukemia was suspected The number of leukocytes was increased to 110 000/mm^3 but the differential count revealed strikingly few immature forms The woman had had severe leukocytosis with a blood histamine content up to 93 μg/100 ml The blood histamine is, on the average much higher in un treated chronic myeloid leukemia The increased serum vitamin B_{12} and the phagocytic activity, as judged by the method of Brandt, might argue for chronic myeloid leukemia The increased alkaline phosphatase score, however, argued against leukemia Valentine et al (18) stressed that the alkaline phosphatase content of the leukocytes and the glycogen content remain increased in polycythemia, even when the blood picture is suggestive of chronic myeloid leukemia

Summary

Sixty four patients with polycythemia were followed with determination of the blood histamine The blood histamine content was determined with a fluorometric method A close correlation was found between the blood histamine content and the number of basophil leukocytes

In 16 of 17 patients with polycythemia vera not treated with ^{32}P the blood histamine content was abnormally high despite normal total leukocyte counts ^{32}P treatment suppressed the blood histamine value The values found in 43 patients treated with ^{32}P varied with the interval after the last treatment and the phase of the disease Two patients treated with phlebotomy showed thereafter normal hemoglobin values but high blood histamine content Four cases of secondary polycythemia showed normal blood histamine values Determination of the blood histamine may be useful in the differential diagnosis between polycythemia vera and secondary polycythemia

During the period of investigation (1 year) acute leukemia developed in 2 of the 43 patients with polycythemia

vera treated with ^{32}P One of these had a remarkably high terminal basophilia The other patient has up to now normal values of basophil leukocytes and blood histamine A third patient had extremely high values of blood histamine and basophil leukocytes and in some respects resembled chronic myeloid leukemia

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Serum Indican in Renal Disease

By

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Indican is a tryptophane metabolite mainly produced in the intestinal canal by the influence of bacteria (5) The use of serum indican as an indicator of renal insufficiency is based on the fact that this substance is mainly excreted in the urine (2 17) Serum indican has been regarded as one of the most sensitive measures of renal failure (9) On the other hand the use of an indicator the formation of which largely depends on the prevailing state of the intestine has been condemned (18) One of the aims of the present study is to discover the significance of an elevated serum indican value in renal failure

There seems to be little correlation between the uraemic syndrome and different biochemical measures It is therefore valuable for the clinician to have a number of laboratory determination to throw light on the condition from different angles In this regard it is likewise valuable to have several NPN substances measured Since indican is one of these, we have studied it from this aspect and tried to examine its correlation with other NPN substances

Thirdly, we wanted to study whether there were some special groups of renal disease in which serum indican differed from other NPN substances of the serum The other NPN substances we have studied are serum creatinine, urea and uric acid

Material and methods

The study was made on a series of 135 patients suffering from acute or chronic renal disease Their distribution according to the main disease groups is seen in table I

At the time of the study five patients were receiving oral antibiotics and 18 antibiotics by the parenteral route Subileus was clinically present in three patients

All the patients in this series exhibited some sign of disturbed renal function This was shown by either a lowered creatinine clearance low concentrating power delayed phenolsulphonphthalein excretion or pathological urography In a great number of the cases the kidney disease was confirmed by a pathological biopsy or necropsy finding

Serum indican was determined in every case The method used was that described by Momas and Schapiro (14) employing the indoxyl thymol reaction The normal value with this method was found to be 0 115 ± 0 012 mg/100 ml The values in

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TABLE I Main diagnoses of the 135 patients included in the study

Chronic nephropathies	
Chronic pyelonephritis	45
Chronic interstitial nephritis	5
Chronic glomerulonephritis	17
Nephrotic syndrome	11
Other nephropathies	3
Total	81
Acute nephropathies	
Acute tubular necrosis	29
Acute oliguric phase of chronic renal failure	16
Acute glomerulonephritis	5
Postrenal anuria	4
Total	54

normal individuals, with healthy kidneys and a normal intestinal state were found to vary within the range 0 05—0 20 mg/100 ml The error of a single determination by this method was ± 0 013 mg/100 ml

Serum creatinine was determined in each of the 135 cases The method used was that of Folin and Wu (8) modified by Brod and Sirota (3) The normal values with this method in our laboratory are 0 7—1 4 mg/100 ml

Serum urea was determined in 90 cases by the urease method of Conway (6) The normal values with this method are 19—36 mg/100 ml

Serum uric acid was determined in 131 cases by the uricase method of Praetorius (16) The values for uric acid with this method are normally 2 6—7 5 mg/100 ml for men and 2 0—5 7 mg/100 ml for women

The values of all NPN substances were determined from samples taken simultaneously on admission

Results

Fig 1 shows the correlation between serum indican and serum creatinine The correlation is strong (r = 0 91) and

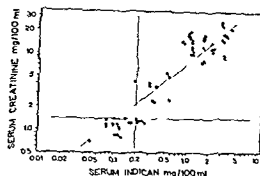


Fig 1 The correlation between serum creatinine and serum indican

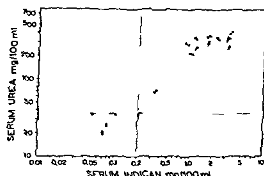


Fig 2 The correlation between serum urea and serum indican

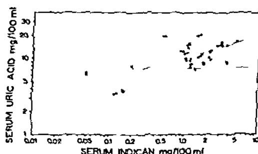


Fig 3 The correlation between serum uric acid and serum indican

is highly significant ($P < 0.001$) There are five patients in whom elevated serum creatinine occurred with a normal serum indican value and four patients in whom the opposite was the case All had a lowered creatinine clearance One of the patients with normal creatinine was a case of poliomyelitis with wasted musculature In the rest no comparable condition could be found No condition

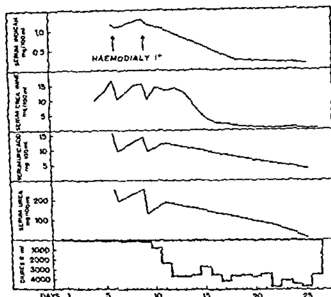


Fig 4 Serum indican creatinine urea and uric acid as well as urinary output in a case of acute tubular necrosis

affecting the indican metabolism, such as ileus or intestinal resection, was present in these cases

Fig 2 shows the correlation between serum indican and serum urea The correlation is strong (r = 0 88) and is highly significant ($P < 0.001$) There are eight patients with elevated serum urea and normal indican and no patients with the opposite

Fig 3 shows the correlation between serum indican and serum uric acid The correlation is relatively strong (r = 0 71) and is highly significant ($P < 0.001$) When the sex dependent differences in the normal values are taken into account there are eight patients with elevated serum uric acid and normal indican while seven patients have the opposite

Acute renal disease

To gain an idea of what happens to the serum indican values in acute tubular necrosis we followed the values of serum indican creatinine, urea and uric acid in the 29 patients with this lesion Fig 4 shows the results in a typical case

Among the cases with acute renal disease there was only one in which, despite a normal serum indican the other NPN substances were decidedly high This was a patient in whom acute tubular necrosis had developed after resection of the ileum and colectomy

Nephrotic syndrome

There were 11 patients with the nephrotic syndrome The serum indican, creatinine urea and uric acid values as well as the creatinine clearance of these patients are presented in table II

As is shown four patients exhibited signs of renal insufficiency indicated by the rise in creatinine urea or uric acid In three of them the creatinine clearance was low By contrast, all the nephrotic patients had a serum indican below the normal mean The mean serum indican for the nephrotics with

TABLE II Serum indican creatinine urea uric acid and creatinine clearances of the 11 nephrotics included in the study

No	Diagnosis	Indican (mg/100 ml)	Creatinine (mg/100 ml)	Urea (mg/100 ml)	Uric acid (mg/100 ml)	Creat clear (ml/min)
1	Glomerulonephritis	0 07	0 85	26 0	4 5	119
2	Glomerulonephritis	0 05	1 05	28 4	8 2	90
3	Glomerulonephritis	0 09	1 10	—	5 9	101
4	Glomerulonephritis	0 05	1 80	75 7	5 2	37
5	Glomerulonephritis	0 04	1 15	17 3	5 2	87
6	Glomerulonephritis	0 03	0 70	33 6	5 6	128
7	LED	0 01	0 90	18 9	5 1	112
8	LED	0 07	1 85	130 8	9 1	86
9	Thrombosis of renal vein	0 11	1 55	58 5	9 1	65
10	Cardiac failure	0 10	3 70	—	8 6	20
11	Unknown	0 08	1 00	—	6 4	109

normal creatinine was 0 053 ± 0,011 mg/100 ml The difference between this and the normal mean (0 115 ± 0 012 mg/100 ml) is statistically significant ($P < 0\ 01$)

Discussion

In order to test the significance of an elevated serum indican value in renal disease, especially in renal failure due to different causes a comparison must be made with well defined measures of this condition It is agreed that the elevation of serum creatinine is one of the most sensitive indicators of renal failure (1, 7, 10) It is true that certain conditions with low creatinine production may exist (13) and, even when combined with renal failure present a normal serum creatinine value (11) Only one patient with such a condition was included in the present series It must also be stressed that in many uraemics with advanced muscular inactivity and wasting, creatinine production may be extremely low In a series like the present one they are numerous, but in the range of low values this fact does not influence the behaviour of the correlation studied It is seen from the results that there are only five cases with elevated creatinine and normal indican and four cases with the opposite situation This means that serum indican and creatinine are of equal significance in this series The conclusion to be drawn is that, from the clinical point of view, the observation of an elevated serum indican usually means renal failure and the absence of such elevation in a suspected case usually indicates that there is no renal failure Furthermore, serum indican appears to offer no advantage over serum creatinine as a measure of renal failure, except in cases with low creatinine production Very slight derangements of function cannot be detected by either method

An equally good correlation exists between the values of serum urea and serum indican It is obvious from the results that there are eight cases with

elevated serum urea and normal indican, while no patient has normal serum urea combined with elevated serum indican This finding indicates that in this series serum urea has been the more sensitive of the two measures for detecting renal failure As was stated before in discussing the material of this study, the patients were suspected to have renal failure on account of low creatinine clearance, low concetrating power, etc In dealing with different cases of renal failure one gains the impression that serum urea is sometimes the most sensitive of the NPN substances measured The present results support this view

When the relationship between serum indican and serum uric acid is examined in this series, it becomes obvious that a correlation is present From the results it may be concluded that for estimating renal failure serum uric acid and indican are of equal value

The fact that such a good correlation exists between serum creatinine urea and uric acid on the one hand and serum indican on the other warrants the use of this measure in renal failure That there was only one case deviating notably affords further support for this view Since serum indican is mainly derived from the intestinal canal, it is to be expected as has been suggested (18) that in renal failure with uraemic manifestations in the gut or in uraemia following intestinal complications the serum indican will not preserve a strict correlation with the other NPN substances To this may be added that in a relatively large proportion of the present cases antibiotics that affect the bacterial flora were used That these circumstances did not disturb the correlation can be explained by assuming that the effect of alteration in the production of indican is small compared with the massive cumulative influence of delayed excretion by the diseased kidneys

The values of serum indican in acute tubular necrosis parallel those of the other NPN substances The only exception is that the dialysis of indican is considerably slower than that of the other three substances This has been demonstrated in a previous paper (15) Whether the slow dialysis has any clinical significance is not clear, the noteworthy observation was that the patients with the slowest dialysis had the poorest prognosis (15) We think that the estimation of serum indican in cases of acute renal failure may be of help in deciding the indications for haemodialysis Without knowing the possible toxicity of an extremely high indican level, we regard it as alarming

The single case not showing the same good correlation as the remainder of this series is instructive It illustrates the specific condition in which serum indican determinations are of no value Thus it must be concluded that indican measurements should not be done in cases where parts of the intestine have been removed

The low indican values in patients with the nephrotic syndrome in the presence of known renal insufficiency is interesting It is known that nephrotics may have increased clearance values for creatinine (4) indicating exaggerated glomerular filtration Indican is known to be excreted partly by glomerular

TABLE II Serum indican, creatinine, urea uric acid and creatinine clearances of the 11 nephrotics included in the study

No	Diagnosis	Indican (mg/100 ml)	Creatinine (mg/100 ml)	Urea (mg/100 ml)	Uric acid (mg/100 ml)	Creat clear (ml/min)
1	Glomerulonephritis	0 07	0 85	26 0	4 5	119
2	Glomerulonephritis	0 05	1 05	28 4	8 2	90
3	Glomerulonephritis	0 09	1 10	—	5 9	101
4	Glomerulonephritis	0 05	1 80	75 7	5 2	37
5	Glomerulonephritis	0 04	1 15	17 3	5 2	87
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From the Medical Department (Head A H Brinchmann) Bærum County Hospital Sandvika Norway

Nephrogenic Erythrocytosis

By

K. Reimers Reksten Jr

Nephrogenic polycythemia (erythrocytosis) is a well established entity In the vast majority of cases reported the renal disorder has proved to be carcinoma The constellation of polycystic kidney disease and polycythemia is far more rare So far 11 cases have been recorded in the literature (2 8 11, 16 18 22) Friend et al (12) have reported on three patients with polycystic kidney disease and a normal hematocrit in spite of uremia But since essential data are omitted from their presentation, these cases cannot be included The authors term the condition relative erythrocythemia (polycythemia)' The same objection applies to the patient of Gurney (13) The case of Cohen (4) included by Remmele (24) in his extensive survey is doubtful The patient had one large cyst in each kidney, probably simple, renal cysts

Even in a few of the 11 above mentioned cases the diagnosis of polycystic kidney disease may be uncertain This is the case when the lesion is unilateral when there are a normal blood pressure and kidney function and when there is no evidence of heredity The diagnosis of polycystic kidney disease may be extremely difficult in the early stages for instance when the disease has manifested itself clinically and roentgenologically in one kidney only The condition may then be indistinguishable from multiple, simple renal cysts (1 6) The correct diagnosis is important, as it has a bearing on therapy and prognosis Renal biopsy could possibly clarify the situation The glomeruli and tubuli in polycystic kidneys show characteristic evolutionary changes (6)

Recently doubt has been expressed as to the consistency of the theory that kidney affections produce a pure erythrocytosis as opposed to polycythemia vera (2) It may, therefore be of interest to report such cases to throw light upon the nature of the blood changes caused by renal lesions

Case report

The patient was a man aged 57 His father died from a kidney disease which manifested itself at the age of 50

Submitted for publication May 12 1964

filtration (12), so that the observed phenomenon might be at least partly explained by this increase in glomerular filtration In our series no case showed a truly enhanced creatinine clearance, which renders the theory invalid The observation that low indican values may exist even in combination with a high serum creatinine demands another explanation The nephrotic patients with tissue oedema may *well have had oedema* of the *intestinal mucosa*, preventing the resorption of the indican produced in the gut It is also possible that the *intestinal flora* in nephrotics is altered so that the production of indican from tryptophane is decreased Whatever the cause of the phenomenon, it must be *concluded that indican measurements* are of little value in estimating renal *failure if the nephrotic component is* considerable

Summary

Serum indican has been studied in patients with renal disease by comparing it with serum creatinine, urea and uric acid Serum indican is of equal significance in measuring renal failure as the other NPN substances studied In cases with low creatinine production, as in muscular disease and wasting, it is superior to serum creatinine *Ileus* and oral antibiotics did not affect the correlation of serum indican with the other NPN substances studied Removal of parts of the intestine *lowers the indican* production so that no significant elevation is observed in renal failure Nephrotic patients have low indican values presumably because of slow absorption from the intestine In acute tubular necrosis serum indican behaves as the other NPN substances studied

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TABLE I The Fe^{59} erythrocyte uptake in transfusion induced polycythemic mice injected with plasma and urine from the patient compared with the uptake in saline injected control mice

	Uptake of Fe^{59} %		
		Mean	S. D
Urine	0 52		
1 ml	0 91		
Inj	0 24	0 82	0 47
Twice	1 49		
(5 animals)	0 94		
Plasma	0 74		
0 5 ml	1 10		
Inj	*5 30*	*3 33*	*2 44*
Twice	6 20		
(5 animals)	3 30		
Control	Range		
Saline	0 22—	0 65	0 38
(21 animals)	1 70		

The patient had been healthy until in May 1960 he was admitted to the Medical Department of Bærum County Hospital, because of several attacks of chest pain The diagnosis of a myocardial infarction was made, and he was placed on long-term anticoagulant therapy Physical examination was normal except for a blood pressure of 160/100 mm Hg The hemoglobin content was 15 7 g/100 ml, the white cell count was 6,000/mm³, the ESR varied between 2 and 4 mm/hour The urine was normal by chemical and microscopical examination the specific gravity was 1,020

In Sept 1960 he was readmitted on account of dizziness and dyspeptic symptoms The blood pressure on admission was 200/120 mm Hg later it was 160/100 mm Hg An X ray of the stomach revealed two duodenal ulcers The hemoglobin content on admission was 16 2 g/100 ml, later 14 8 g/100 ml The white cell count was 7,200/mm³ the ESR varied between 1 and 5 mm/hour The serum creatinine was 1 3 mg/100 ml Urinanalysis was negative, the specific gravity being 1,015 He made an uneventful recovery

He was hospitalized the third time in March 1963 with a two months history of paroxysmal flushing and heating of the face Four weeks prior to admission he had had a sudden attack of pricking, paresthetic sensations in the left side of the head and the face and the left arm and leg, followed by numbness He had not noted any paralysis

On admission the symptoms had subsided, but his face had a somewhat flushed appearance Initially the blood pressure was 180/120 mm Hg and after three weeks the diastolic pressure still varied between 100 and 120 mm Hg There were no biochemical evidences of a pheochromocytoma or a carcinoid tumor An X ray of the skull was normal and so was the cerebrospinal fluid An EEG was normal, but a neurological examination pointed to a vascular lesion in the right hemisphere, probably of thromboembolic origin

The urine now contained traces of protein, but still no sediment, the specific gravity was 1,020 The serum creatinine varied between 1 2 and 1 4 mg/100 ml

A hematological study gave the hemoglobin content as 20—17 8—19 7—19 7 g/100 ml the red cell count as 5 94—6 27—6 40 mill/mm³ A blood smear was normal The ESR varied between 1 and 5 mm/hour The hematocrit (van Allen) was 55 % The white cell count was 7 600/mm³ The platelet count was 164,000/mm³ The total blood volume determined by the radioiodinated albumin method was 4 900 ml (75 6 ml/kg body weight) where the red cell volume was 2 480 ml (38 3 ml/kg), and the plasma volume 2 420 ml (37 3 ml/kg)

An urogram revealed bilateral polycystic changes This was confirmed by urography and tomography after retroperitoneal air insufflation At this time both kidneys could be felt bimanually The liver and the spleen could not be felt

The patient was discharged without special treatment

In Oct 1963 he was readmitted because of intermittent weakness a feeling of heaviness in the head dizziness and a tendency to faint There was a moderate hypertension the serum creatinine was 1 4 mg/100 ml, the hemoglobin content was 20—17 8 g/100 ml, the red cell count was 6 30 mill /mm³, the hematocrit was 56 %. A phlebotomy of 500 ml was performed which brought about some relief of the symptoms

The plasma and the urine were bioassayed for the erythropoietin content Transfusion induced polycythemic mice were used as recipients and Fe^{59}-erythrocyte uptake as parameter as described by Rosse et al (25) except that the 72 hour instead of the 48 hour uptake was used The result is showed in table I In the urine no increase in erythropoietin could be demonstrated while the plasma erythropoietin level was slightly elevated The mean uptake in mice who received plasma was 3 3 % compared with 0 65 % in saline control mice The difference between the plasma and the control group was tested by a Mann Whitney U test which gave U = 9 5 P < 0 01

Discussion

The positive family history, the elevated blood pressure and above all the typical roentgenological findings confirm the diagnosis of polycystic kidney disease in this patient beyond reasonable doubt

The blood changes were not pronounced yet the diagnosis of polycythemia (erythrocytosis) seems quite certain According to Wintrobe (26) the upper normal limit for hemoglobin is 18 0 g 100 ml for the red cell count, 6 2 mill mm³ and for the hematocrit vol 54 0 %. These values were exceeded on several occasions The most significant finding however was the red cell volume This was clearly elevated, namely to 38 3 ml/kg the upper normal value being 35 0 ml/kg

As in several of the reported patients, an elevated plasma level of erythropoietin could be demonstrated in the patient, in spite of moderate blood changes

The effect of erythropoietin on the red cell production only is now universally recognized hence its designation This result is mainly based on animal experiments made by Jacobson et al (15) and other workers Keighley et al (17) make special mention of the lack of effect on the white cells and the platelets Hammond and Keighley (14) have also demonstrated the absence of such an effect in patients suffering from aplastic anemias These patients had for years elevated plasma levels of erythropoietin, but persistently normal values of white blood cells and platelets (17)

In accordance with this, most authors have reported normal values of white cells and platelets and no spleen enlargement, in patients with nephrogenic polycythemia The term erythrocytosis' therefore, seems to be more appropriate The patient described above fits well into this picture

There are however exceptions to this rule Among the cases of Brandt et al (2) there were 8 with supposed nephrogenic blood disorders No less than 7 of these featured one or more of the signs usually found in polycythemia vera According to the authors, it is difficult to sustain the theory that kidney affections produce erythrocytosis only

There are a few reports of patients with one or more of the findings usually associated with polycythemia vera (leu

cocytosis, thrombocytosis and splenomegaly), in whom these findings have disappeared after surgical treatment (3, 5, 7, 9, 10, 21). For instance the patient of Martt et al. (21) had splenomegaly and a moderate leucocytosis, which subsided after nephrectomy. Such reports, however, are remarkably few, and frequently the patients have not been adequately investigated postoperatively.

There is some experimental evidence, albeit awaiting definite confirmation, that erythropoietin is not the sole hormone operative in the regulation of hematopoiesis. It is probable that some substance with different biochemical characteristics exerts an influence upon the production of the white cells and the platelets. It has been demonstrated that plasma from patients suffering from polycythemia vera has a stimulating effect on both the white cells and the platelets in normal rats. The plasma of rats made anemic by means of phenylhydrazine usually contains large amounts of erythropoietin. If heated, extracts of such plasma will cause leucocytosis and thrombocytosis in normal recipient rats (19, 20).

Turning to human pathology, it has been known for some years that not only the plasma, but also renal cyst fluid and cyst wall, as well as tumor tissue, may contain large amounts of erythropoietin (13, 22). But recently Race et al. (23) have demonstrated a platelet-stimulating factor in cyst fluid from a cerebellar hemangioblastoma, a tumor well known for its polycythemia-producing properties. No effect on the white cell count was noted.

So there are several outstanding points to be clarified, and it is therefore still of interest to report on cases of nephrogenic blood disorders, if they have been submitted to a complete hematological investigation. Well documented cases of polycythemia vera cured by nephrectomy will be of particular interest.

Summary

A patient featuring the combination of polycystic kidney disease and erythrocytosis is described. In the light of clinical and experimental evidence the nature of the blood changes, polycythemia vera versus erythrocytosis, is discussed.

Acknowledgement

I am indebted to Dr. Sverre Halvorsen and Dr. Per Haavardsholm Finne, Pediatric Research Institute, University Hospital, Oslo, who performed the bioassay for erythropoietin.

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From the First Department of Medicine (Head Pentti I Halonen, M D),
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Abnormal Circulatory Responses to Exercise as Sequelae to Encephalitis

By

M H Frick, G Hartel and Sven Punsar

In addition to reflex mechanisms mediated at medullary and spinal levels, the neural control of the heart includes also supramedullary activity The evidence for this is largely based on electrical exploration of the central nervous system data of which are abundant in contrast to the scanty information of clinical medicine Apart from the cardiovascular effects of central nervous system tumours and acute infections (1) attention has been paid to subendocardial haemorrhages found in association with intracranial lesions (10) and to intestinal haemorrhages which frequently follow pathological processes in the anterior hypothalamic region (12) Electrocardiographic abnormalities following subarachnoid haemorrhages are also an established item (7)

The present case illustrates a functional cardiac abnormality together with neurological sequelae of encephalitis

Submitted for publication May 13 1964

Case report

The patient a 51 year-old foreman was first seen by us in June 1963 He was sent for cardiological examination because of his dyspnoea of effort and calcification along the upper right border of the heart detected by mass X ray

As a child he had had right sided pneumonia with empyema which was treated by drainage Another attack of pneumonia occurred in 1946 with complete recovery

In 1937 he had suffered for three weeks from a marked right-sided headache and fever up to 38.0 C After a short period of dizziness nausea and diplopia to the right side he was admitted to the hospital of the Finnish Red Cross Examinations revealed a small right pupil of irregular shape which reacted poorly to light stimuli There was paresis of the medial rectus muscle of the right eye The ocular fundi were normal as was the cerebrospinal fluid The right side of the face was hypoaesthesic and there was a tendency to fall to the left It was judged that the patient had several scattered foci of inflammation in the central nervous system especially in the cerebellum With

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Fig 1 Catheter in right atrium against the lateral wall illustrating the pericardial origin of the calcification

symptomatic treatment his condition gradually improved He was later, however re-admitted twice to the same hospital because of symptoms similar to the above combined with loss of memory and decreased sexual potency The EEG was normal as was an arteriogram made in the right internal carotid artery A pneumoencephalogram showed intracranial adhesions

Since his last neurological examination in 1942 he had periodically suffered from headache dizziness and tremor in the right hand Starting from 1962 he had experienced effort dyspnoea and palpitations especially at night He was distressed by substernal pain on effort but not regularly He was able to rise one floor without resting

Physical examination The nutrition was average His walk was staggering and Romberg s test showed falling to the left The pupils were small and unresponsive to light The left patellar reflex was clonic, the right slow and weak The Babinski sign was negative on both sides There was a fine tremor in both hands, more in the right A small nodule was palpable in the right lobe of the thyroid BP was 145/85 Pulse rate was 70 beats/min and regular The apex beat of the heart was not palpable the right ventricle was not heaving A systolic grade two ejection type murmur was audible at the base of the heart and was not transmitted to the neck

Laboratory findings Hb 13 5 g/100 ml, erythrocytes 4 49 mill /mm³, packed cell vol 42 %, leucocytes 9 400/mm³ with normal differentiation, ESR 8 mm/h, blood Wasserman reactions negative, cholesterol 328 mg %, PBI 6 2 μ %, plasma creatinine 1 08 mg %, serum sodium 141 mEq/l, potassium 4 5 mEq/l, chlorides 101 mEq/l, calcium 10 3 mg %, AST 32, ASTA 0 8, Toxoplasma reactions negative, cerebrospinal fluid Pandy-, Nonne-, sugar 58 mg %, 1 cell/ml, urinary excretion of catecholamines 75 μg/24 h and of vanillin mandelic acid 4 1 mg/24 h Skin biopsy not diagnostic

X ray findings Radiograph of the chest showed bilateral adhesions in the costophrenic angles but nothing else abnormal in the lungs The heart was of normal shape and volume (480 cm³/M) A sickle shaped calcified shadow was located along the outer border of the right auricle (fig 1) Kymogram showed diminished pulsations at this area Radiograph of the stomach revealed a slightly irritated ventricular mucosa but no ulcers or paraoesophageal hernias

Cardiological studies ECG sinus rhythm 60 beats/min semihorizontal position P—Q 0 16 sec Q—T 0 38 sec No signs of ventricular or atrial hypertrophy No signs of ectopic pacemakers or sino-atrial and atrioventricular block at rest or during exercise The oxygen saturation of the arterial blood was normal at rest and during exercise Respiratory functions showed a slight restriction the vital capacity and forced expiratory volume being 80—90 % of normal Maximal breathing capacity was over 100 % and the expiratory peak flow 100 % Blood gas analyses revealed respiratory alkalosis at rest accentuated during effort

TABLE I Haemodynamic response to exercise and isoproterenol

	Pulse rate, (beats/min)	Stroke volume (ml)	Cardiac output (l/min)	Brachial art pressure (mm Hg)
Rest legs on pedals	63	106	6 97	148/80
200 kpm/min	90	126	11 56	164/80
400 kpm/min	102	212	21 60	182/88
Before isoproterenol	70	132	9 25	140/80
5 min after isoproterenol	72	128	9 20	144/82
10 min after isoproterenol	78	116	9 07	148/88

The physical fitness was tested on four different occasions by an electrically braked bicycle ergometer in both supine and sitting position always with the same curious finding that the pulse rate could not be raised with effort over a limit from 114 to 120 beats/min At this level of pulse rate the patient was exhausted he was dyspnoeic and complained of extreme weakness of the legs forcing him to stop pedalling The external work load necessary to raise his pulse rate to this speed limit was in every instance 400 kpm/min Atropine subcutaneously in a dose of 2 mg elicited no response until after 25 min with a rapid and transitory rise from 68 to 92 beats/min The pulse rate response to 20 mg isoproterenol sublingually was an increment of 6 beats/min after 10 minutes No abnormal pulse rate or blood pressure reactions were noted on changing from recumbency to standing To study this circulatory abnormality further and to confirm the location of the calcification observed in the chest X ray cardiac catheterization was performed The pressures were normal throughout the right side of the heart and the pulmonary artery and the oxygen values excluded shunts The position of the catheter in the right atrium in relation to the calcification is illustrated by fig 1

During the catheterization exercise responses were studied on external work loads of 200 and 400 kpm/min utilizing dye dilution and pulmonary artery injections On the same occasion the effect of 20 mg of isoproterenol sublingually was also evaluated starting 10 min after the exercise was stopped The relevant data are compiled in table I

The patient was later readmitted for assessment of his eligibility for a pension On this occasion the above listed studies on the haemodynamic response to exercise were repeated and the cardiac output measured by the Fick principle The results were basically the same as before however the pulse rate increased from a resting value of 66 beats/min to 120 at a load of 200 kpm/min and declined to 102 beats/min at the following load of 400 kpm/min a highly pathological finding The oxygen uptake measured by the Douglas bag technique was compatible with our results on healthy volunteers The neurological examination was completed with an EEG which showed diffuse dysrhythmia

Discussion

The circulatory pattern in this patient was not compatible with the well known effects of a preponderance of one of the autonomic nervous systems The resting pulse rate was not low and the response to atropine was weak and doubtful Further, the bradycardia due to enhanced vagal tone tends to be

abolished during exercise if not due to physical training (5) Neither was the resting pulse rate compatible with sympathetic stimulation, and the pulse rate response to exercise was not concordant with the vagus — sympathic interrelations during exercise (8) The circulatory response to exercise was different from that obtained after blocking of the vagus or sympathic selectively or both together (3, 6) The chronotropic effect of isoproterenol was of the magnitude we have been accustomed to, but the inotropic effect with decreased stroke volumes was atypical since a positive inotropic effect has been demonstrated even on a failing myocardium (4) In retrospect, however, the rather short interval between the cessation of exercise and the administration of the drug might have had some influence

Cardiac catheterization and dye dilution studies, originally undertaken to clarify whether the pericardial calcification mechanically interfered with the atrial contribution, revealed that the stroke volume was the major determinant in increasing the total blood flow This type of regulation has been shown to exist in dogs with experimentally created complete atrio-ventricular block (11) and in humans with the same condition (2) In patients with sinus rhythm this circulatory pattern has not been reported to our knowledge

Connections to the central nervous system are evident, but the solution remains elusive A rather striking similarity, however, can be found to exist with one of the experiments of Smith et al (9), who produced lesions in the hypothalamic region and observed a restriction of the pulse rate response to exercise, together with increased left ventricular diameters in a dog

Apparently, when the stroke volume is the major factor in enhancing the blood flow, the capacity of the heart is reduced to a maximal delivery of about 100 per cent over the resting flow multiplied by the heart rate contribution If the rate response is markedly limited, as in the present case, the circulation is inferior to its task in strain situations, a feature familiar from patients with complete atrio ventricular block

Summary

The clinical and haemodynamic features of a case with neurological sequelae of encephalitis are described The haemodynamics were characterized by a limited pulse rate response to exercise, forcing the stroke volume to be maximally augmented Effort dyspnoea and fatigue became manifest at a cardiac output level of 21 6 l/min the value for the heart rate being 102 beats/min and for the stroke volume 212 ml The heart was in sinus rhythm throughout the experiments and its rate could not be increased over a value of 120 beats/min by means of muscular exercise or pharmacological agents

Acknowledgement

Supported by a grant from the Yrjo Jahnsson Foundation

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Due to an unfortunate mistake the pages 768 and 800 have accidentally been omitted in the printing of Volume 176, Fasc 6 The missing two pages are enclosed herewith, and we would like to take this opportunity to express our sincere regret for the mistake which we hope will not have caused you too much inconveniency

Stockholm January 26 1965

AB P A Norstedt & Söner
Printers of the Acta Medica Scandinavica

Book review

ledical Annual A Year Book of Treatment and Practitioners' Index Eighty second Year John Wright & Sons Ltd, Bristol 1964

he Medical Annual is always re ived with keen expectancy It presents cross section of the most important ents during the past year and although ur contributors change it always main ains the same high standard

This year s edition tarts with a special rticle on the transport of patients by air, question of growing importance in iew of the constant increase of air traffic hich has recently come up for discus ion on different occasions

Fully in conformity with the growing nterest for immunology and the changed pinion this has brought concerning ertain diseases and of groups of diseases, another special article is devoted to "Auto immunity as a Cause of Disease

Quick and satisfactory results without side effects are reported from the treat ment of cardiac arrhythmias and restora tion of rhythm by direct current counter shock

A couple of hundred patients had been treated during the year with very good results by reconstructive procedures for renal artery stenosis as a cause of hypertension It is important that the correct diagnosis is made and the opera tion performed before irreparable hanges occur

Reference is made to Leksell s epochal contributions within brain surgery, the latest of which, as is known, is the use of a proton beam

In the last two numbers of Medical Annual a new drug against smallpox has been named, N methyisatin thiosemicar bazone (Compound 33T57, marboran) A preliminary report now exists from Madras, India of the use of this chemotherapeutic as a form of prophylactic treatment for smallpox contacts Marboran in a dose of 3 g daily for 4 days was given to a group of 1101 persons There were only 3 cases of smallpox all mild among these close contacts, whereas there were 78 cases of smallpox with 12 deaths in a control group of 1 126 contacts altogether irrespective of vaccination status If these results are confirmed, it means an enormous advance in the combating and prevention of the spread of smallpox, the greatest since the days of Jenner It would also mean that we have now for the first time acquired a drug which has an assured effect against a viral infection, even if only as a prophylactic

An interesting point is that the British Pharmacopoeia has now changed to the metric system

These are just a few glimpses from this excellent book

Birger Strandell
Stockholm

Acta Medica Scandinavica Vol 176, fasc 6, 1964

From the Medical Clinic of the University of Pisa, Pisa Italy

Clinical Applications of Quantitative Radiocardiography

I Results in Normal Subjects and Changes with Age

By

Attilio Maseri, Victorio Pecorini, Pietro Toni, Giovanni Micheli and Luigi Donato

Quantitative radiocardiography permits the measurement of cardiac output and of the volumes of blood in the pulmonary circulation and in the right ventricle, from the analysis of the curves recorded by a precordial counter during the passage of a γ emitting tracer through the cardiopulmonary circulation

This technique has been developed in recent years in the Center of Nuclear Medicine of the University of Pisa (1 8 14 22) and recently improved by its combination with right cardiac catheterization (9 10 11 15 19) The theoretical foundations of the method and its possibilities have been previously examined (9 10 11 15 19) the values for cardiac output pulmonary and right ventricular blood volume are in close agreement with those obtained by other investigators with different techniques (7 13 16 17 21 25)

Sequential measurements of cardiac output and pulmonary blood volume at the bedside obviously might be helpful in connection with some clinical emergencies such as acute left ventricular failure, myocardial infarction shock and hypertensive seizures as well as in assessing hemodynamic changes induced by treatment of cardiocirculatory diseases It is obvious, however, that regular application of radiocardiography as a clinical method would be seriously limited by the need for heart catheterization

With the aim of overcoming this limitation a special portable counting unit has been set up and the technique has been modified avoiding right-cardiac catheterization for the injection of the tracer so as to permit an easy performance of the test at the bedside, without sacrificing accuracy

Instrumentation and technique will be described in this paper and the results obtained in a group of normal subjects aged from 17 to 83 years will be illustrated

Submitted for publication June 5 1964

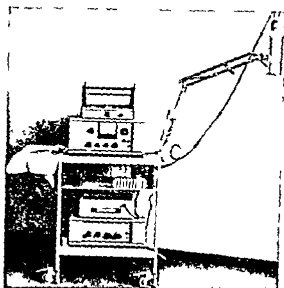


Fig 1 The instrumentation employed For description see text

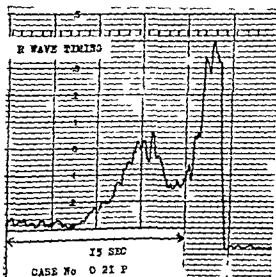


Fig 2 The original RCG of case No 021 with superimposed the R wave timing of the ECG Full scale 300 000 counts per min Time constant of 0 05 sec

Methods

Instrumentation

The instrumentation consists of a counting ratemeter (Tracermatic SC-71) with amplifier and pulse analyzer (Tracermatic SC 76), a rectilinear dual direct writing recorder (Texas Instr Inc) and an electrocardiograph placed on a carriage to which a movable arm, holding at its end the scintillation probe, is attached (fig 1) The probe consists of a 1 5 inch NaI (Tl) crystal and a photomultiplier (RLD 2 Tracerlab) housed in a cylindrical lead collimator of the same diameter, and recessed 80 mm from the external opening

Technique

The probe is positioned 1 cm away from the anterior chest wall at the level of the fourth intercostal space on the left sternal border

The tracer, about 50 μC of radioiodinated human serum albumin ($RI^{131}HSA$) (free iodine < 1 %) diluted in saline, is injected into the superior vena cava or into brachiocephalic vein through a polyethylene tube having a total capacity of 0 25 ml threaded into the median vein through a needle

From a reservoir syringe, the volume to be injected is drawn, via a 3 way stopcock, into a calibrated syringe (B D Cornwall luer lok Syringe No 1250S) adjusted to deliver a volume of 0 2 ml whence it is transferred into the polyethylene tube which is then clamped at its proximal end

Injection is made by flushing the polyethylene with 0 5 ml of saline delivered from another calibrated syringe

This procedure has been found very effective in flushing instantaneously and completely the tracer into the circulation The injection can be repeated several times leaving the polyethylene tube "in situ" 0 1 ml of air then being introduced before the dose to prevent dilution of the injectate with the fluid contained in the tube

The precordial radioactivity changes are recorded simultaneously with an electrocardiographic lead using a paper speed of 12 inch min and a time constant of 0 05 sec that does not induce appreciable delay in the inscription of the tracing the distortion due to the direct writing system being negligible

Five min after the injection of the tracer a precordial activity level is recorded with a time constant of 1 sec and a paper speed of 0 75 inch min and a venous blood sample

is taken to obtain the hematocrit value and the plasma concentration of RIHSA For this purpose the activity of 1 ml of plasma is determined in a well counter

A volume of RIHSA solution equal to that injected for a single curve is quantitatively diluted with saline (1/1 000) and the activity of 1 ml is then determined in the same well counter

Cardiac output (CO) is computed according to the following formula

$$CO = \frac{\text{final level (cpm) HF}}{\text{Area (cpm min)}} BV$$

where the area of the radiocardiogram is completed by semilog extrapolation of the descending limb of the left curve (fig 3) the final level is recorded 5 min after the injection of the tracer and represents the net increase of the radioactivity over the precordium HF is an experimental factor for the extracardiac activity contributing to the final level (19) it is essentially constant from one case to another averaging 0 83, *BV* is the distribution volume of the RIHSA at 5 min that can be approximately identified with the true blood volume of the subject It is calculated from the body hematocrit (4) and plasma volume the latter being the ratio of the injectate to the plasma concentration at 5 min

The pulmonary circulation time ($\overline{PCT}$) is computed in heart cycles as the average of minimum and maximum transit time (9) (fig 3)

The pulmonary blood volume (PBV) is obtained as the product of $\overline{PCT}$ in heart cycles and the stroke volume (SV) that represents the flow per heart cycle

The volumes of blood contained in the right ventricle were not measured because although the injection of the tracer into the superior vena cava does not influence appreciably the determination of $\overline{PCT}$ (19) it does not allow the correct measurement of the systolic emptying rate of the right ventricle as the arrival of the tracer into the ventricle might not be complete in one or two heart cycles (9)

Each subject was given 20 drops of Lugol solution before the study to prevent radio-

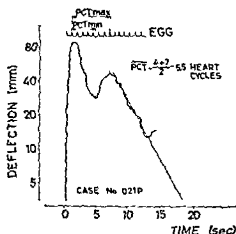


Fig 3 The same tracing as in fig 2 represented on semilogarithmic paper one mm deflection = 2 630 counts per min The left curve has been completed by extrapolation PCT_{min} and PCT_{max} = minimum and maximum pulmonary circulation time $\overline{PCT}$ = mean pulmonary circulation time

iodine uptake by the thyroid The integral radiation dose received by a subject for one injection is of the order of 0 1 rad

Material

Thirty nine patients (11 female and 28 male, average age 49 5 years) were studied

They had been hospitalized at least a week before the study and submitted to clinical X ray and ECG examination in none were cardiovascular or pulmonary abnormalities found Most of them were studied immediately before discharge

According to their ages the subjects were divided into 4 groups

The first group is composed of 14 subjects (4 female and 10 male) aged from 17 to 39 average 25 9 years

The second group is composed of 9 subjects (3 female and 6 male) aged from 40 to 59 average 50 3 years

The third group is composed of 9 subjects (2 female and 7 male) aged from 60 to 69 average 64 1 years

TABLE I The values for arterial pressure (A P), plasma volume (Pl V), blood volume (BV), hema-time ($\overline{PCT}$), and pulmonary blood volume (PBV) *in a group of 39 cardiovascular normals*

Case	Diagnosis	Sex	Age	BSA	A P (mm Hg)
003 P	Cystitis	♀	21	1.48	120/65
007 P	*Glomerulonephritis without functional renal impairment*	♂	*22*	*1.76*	*140/90*
009 P	Cardiac neurosis	♂	34	2.00	130/80
016 P	Mild fever of unknown origin	♂	42	1.88	120/80
017 P	Microhematuria	♀	25	1.44	125/70
019 P	Mild bronchial asthma	♂	19	1.73	115/70
021 P	Peptic ulcer	♂	62	1.62	125/75
022 P	Resolving bronchitis	♂	55	1.84	115/70
023 P	Mild fever of unknown origin	♂	17	1.77	130/80
026 P	Mild fever of unknown origin	♂	22	2.00	125/80
029 P	Peptic ulcer	♂	40	1.69	135/85
030 P	*Resolving broncopneumonia*	♂	*80*	*1.69*	*140/90*
033 P	Pleurisy	♂	27	1.62	125/70
035 P	Cervicoarthrosis	♂	53	1.80	150/90
037 P	Pyelonephritis without functional renal impairment	♂	*19*	*1.78*	*120/80*
050 P	Atonic colon	♂	*83*	*1.70*	*165/90*
053 P	Resolving broncopneumonia	♂	74	1.74	150/70
055 P	Proteinuria	♂	51	1.57	130/75
061 P	Lumbarthrosis	♂	71	1.83	175/90
065 P	Cervicoarthrosis	♂	63	1.80	110/60
067 P	Pleurisy	♂	33	1.90	155/90
068 P	*Colecystitis*	♀	*41*	*1.75*	*135/80*
069 P	Prostatic hyperplasia	♂	66	1.76	160/90
070 P	Pleurisy	♂	37	1.80	140/75
071 P	Colecystitis	♀	22	1.72	125/80
073 P	*Renal stones*	♀	38	1.80	*130/90*
074 P	Gastroduodenitis	♂	26	1.78	125/85
078 P	Mild diabetes	♂	65	1.84	145/80
079 P	Microhematuria	♀	63	1.68	160/90
080 P	Irritable colon	♀	80	1.63	145/70
081 P	Gastroduodenitis	♂	78	1.67	160/93
082 P	Lumbarthrosis	♂	61	1.76	150/95
083 P	Pleurisy	♀	71	1.71	170/90
084 P	Renal stones	♂	64	1.82	140/85
085 P	Irritable colon	♂	67	1.81	150/90
089 P	Colecystitis	♀	66	1.73	160/90
091 P	Pleurisy	♀	59	*1.78*	*120/75*
092 P	Peptic ulcer	♂	58	1.72	135/80
093 P	Colecystitis	♀	54	*1.68*	*145/90*
	Mean	—	49.5	1.74	—
	S D	—	20	0.11	—

tocnt (Hc) heart rate (HR) cardiac index (c i) stroke volume (SV) pulmonary mean circulation

Pl V (ml/kg)	BV (ml/m²)	Hc (%)	HR (1/min)	c i (l/min/m²)	SV (ml)	$\overline{PCT}$ (heart cycles)	PBV (ml)	PBV/m² (ml/m²)	PBV/BV (%)
40	2 433	37	68	4 0	82	—	—	—	—
48	2 862	37	79	3 9	87	5 5	479	272	9 5
39	2 536	39	66	3 3	101	6 0	606	303	12 0
43	2 507	38	88	3 3	71	6 0	426	227	9 0
4?	2 686	40	70	3 0	62	5 5	341	237	8 8
47	2 697	39	67	3 1	79	5 5	435	251	9 3
39	2 618	37	70	3 0	70	5 [illegible]	385	238	9 1
40	2 573	43	76	3 2	77	6 0	462	251	9 8
39	2 626	39	80	4 1	91	5 5	501	283	10 8
42	2 633	39	76	4 2	10[illegible]	5 5	578	290	11 0
39	2 515	42	73	3 1	71	6 0	426	252	10 0
35	2 644	40	58	2 1	64	6 0	384	227	8 6
43	2 600	39	71	3 2	70	5 5	385	238	9 1
44	2 810	43	70	2 8	74	6 5	481	267	9 5
45	2 703	44	76	3 8	89	—	—	—	—
48	2 374	31	72	2 2	55	7 0	412	243	10 0
42	2 277	34	54	2 0	64	6 0	384	221	9 5
38	2 468	39	79	3 5	71	5 [illegible]	392	250	11 9
47	[illegible] 364	32	53	2 7	96	5 0	480	262	11 1
38	2 483	44	[illegible]6	2 8	88	6 0	[illegible]28	293	11 8
46	2 860	40	62	4 0	122	5 0	610	321	11 2
38	[illegible] 743	41	75	3 6	84	5 5	462	264	9 6
40	2 643	36	67	2 6	68	6 0	403	231	8 [illegible]
45	2 662	37	68	3 2	85	6 5	553	307	11 [illegible]
44	2 72[illegible]	39	78	3 0	66	7 0	462	269	9 8
41	2 672	40	60	3 5	10[illegible]	5 0	525	292	10 9
40	2 657	40	74	3 2	77	6 0	462	260	9 8
38	2 601	40	62	2 9	86	5 5	4[illegible]3	258	10 0
41	2 [illegible]68	36	8?	3 4	70	6 5	455	271	10 5
43	2 [illegible]	3[illegible]	61	2 7	78	5 5	429	263	8 9
36	2 450	38	51	2 2	72	—	—	—	—
35	2 31?	38	60	2 [illegible]	73	6 0	438	249	10 8
42	2 471	31	77	3 0	67	6 5	434	254	10 3
37	2 412	39	74	2 9	71	6 5	461	253	10 5
43	2 527	38	60	2 9	73	5 5	401	222	8 8
40	[illegible] 809	37	[illegible]0	2 6	62	5 5	49[illegible]	286	10 1
33	2 430	37	63	2 7	76	6 0	456	256	10 8
41	2 493	33	59	2 6	76	6 5	494	287	11 5
4?	2 570	36	61	3 0	82	6 0	492	293	11 4
41 ?	2 589	38.3	65 8	3 1	78 5	5 9	461	262 3	10 1
3 4	153	3 1	14 2	0 53	13 8	0 5	63	25 3	1 0

TABLE II The mean values of the considered parameters in the 4 age groups Same abbreviations as in table I

Group	Age	BSA (m²)	Pl V (ml/kg)	BV (ml/m²)	Hc (%)	HR (1/min)	c i (l/min/m²)	SV (ml)	$\overline{PCT}$ (heart cycles)	PBV (ml)	PBV/m² (ml/m²)	PBV/BV (%)
I	25 9	1 75	42 9	2 688	39 2	71 1	3 54	87 2	5 7	495	277	10 3
II	50 3	1 75	40 4	2 570	39 7	71 6	3 10	75 8	6 0	455	261	10 4
III	64 1	1 76	39 0	2 554	38 3	64 6	2 84	72 3	5 9	449	256	10 0
IV	76 7	1 71	41 7	2 507	34 5	60 9	2 41	70 9	6 0	420	245	9 7

The fourth group is composed of 7 subjects (2 female and 5 male) aged over 70 years, average 76 4 years

Most of them were studied in the morning, the remainder in the afternoon, at least 5 hours after the last meal

Results

Only in three radiocardiograms did the right curve show a slow rise and a reduced height, probably due to misplacement of the catheter tip into a collateral vein, yet, the final extrapolation of the left curve was easy, although $\overline{PCT}$ could not be measured owing to the poor separation of the right and left curves In all the remaining radiocardiograms the peak of the right curve was *reached* in one or two heart cycles and the separation of the right and left *curves was excellent (fig 2) No patient* showed any distress during or after the performance of the study

The results obtained are reported in detail in table I, in table II the mean values of the *various* parameters for each group are reported

Blood volume has been referred to body *surface* area and was on the average 2,588 ± 153 ml/m², in the four groups it was respectively 2,688, 2,570, 2,554 and 2,507 ml/m², *showing a decrease* of 2 5 ml/m² per year (r = 0 32 P < 0 005)

Cardiac index was on the average 3 1 ± 0 5 l/min /m², being in the four groups respectively 3 5, 3 1, 2 8 and 2 4 l/min /m², decreasing by 21 ml/min /m² per year (r = 0 78, P < 0 001) Also the stroke volume showed a decrease of 0 3 ml per year (r = 0 42, P < 0 01)

Pulmonary circulation time was on the average 5 9 ± 0 5 heart cycles with only small variations among the four groups, respectively 5 7, 6 0, 5 9 and 6 0 heart cycles

Pulmonary blood volume was on the *average 461 ± 63 ml corresponding to* 262 ± 25 ml/m² It appeared closely correlated with body surface area (b = *427*, r = *0 72*, *P < 0 001*) *and* with stroke volume (b = 3 6, r = 0 81, P < 0 001) and less closely with cardiac output (b = 0 024, r = 0 50, P < 0 01) and with blood volume (b = 0 07, r = 0 43, P < 0 01) In the four groups

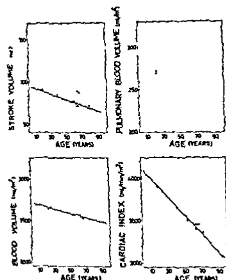


Fig 4 The values for stroke volume (SV) pulmonary blood volume (PBV) blood volume (BV) a d cardiac index (c i) are represented versus age SV = 94—0 29 years r = 0 42 P < 0 01 BV/m² = 2 711—2 48 years r = 0 32 P < 0 05 c i = 4 209—21 years r = 0 78 P < 0 001 No correlation was found between PBV/m² and age

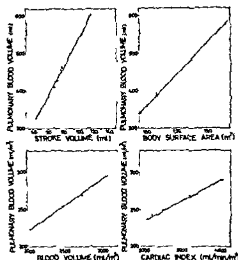


Fig 5 The values for pulmonary blood volume are represented versus stroke volume body surface area blood volume and cardiac index PBV = 179 + 3 6 SV r = 0 81 P < 0 001 PBV = 285 + 426 6 BSA r = 0 72 P < 0 001 PBV/m² = 80 8 + 0 07 BV/m² r = 0 43 P < 0 01 PBV/m² = 189 + 0 024 c i r = 0 50 P < 0 01 Same abbrevations as in fig 4

it was respectively 277 261, 256 and 245 ml/m² No significant correlation was found between PBV/m² and age The ratio PBV/BV was on the average 10 1 ± 1 0 being in the four groups respectively 10 3 10 4, 10 0 and 9 7

In fig 4 the values for blood volume cardiac index, stroke volume and pulmonary blood volume are represented versus age and in fig 5 the values for pulmonary blood volume are represented *versus* body surface area stroke volume, cardiac index and blood volume

Discussion

The modifications introduced in the technique while permitting an easy application to clinical routine do not prevent the gathering of valuable hemodynamic information

In fact the calculated values for blood volume and cardiac output are in the accepted normal ranges and the values for pulmonary blood volume are in close agreement with previous reports (table III) Cardiac output has been previously compared with that found by the peripheral injection method (23) and the results were quite satisfactory While the decrease of blood volume with age is slight in agreement with previous reports (5, 24) cardiac index shows a marked reduction The value of the regression coefficient *in our series* (21 ml min /m²/year) agrees well with that of Cournand et al (26 2 ml/min /m²/year) (6) and Brandfonbrener

TABLE III Values reported by different authors for pulmonary blood volume (PBV)

Authors	Subjects		Method	PBV/m² (ml)
	No	Type		
Kunieda (17)	23	Rheum heart disease	Double injection technique	350
Milnor et al (21)	19	Rheum heart disease	Double injection technique	365
Dock et al (7)	45	Rheum heart disease	Double injection technique	322
Lewis et al (19)	18	Normal	Quantitative radiocardiog	313
Bianchi et al (2)	32	Normal	Quantitative radiocardiog	281
Varnauskas et al (25)	32	Rheum heart disease	Double injection technique	310
Giuntini et al (15)	17	Normal	Quantitative radiocardiog	293
Present study	39	Normal	Quantitative radiocardiog	262

et al (24 4 ml/min /m²/year) (3) These data are also in good agreement with those of Lammerant (18) The reduction of cardiac output is accounted for by a decrease both of stroke volume and heart rate The reason for this fall, which exceeds that of oxygen consumption and of total body water (3), is still uncertain It is possible that younger subjects were more apprehensive than older subjects and consequently they had higher heart rate and cardiac output

The pulmonary circulation time expressed in heart cycles shows only small variations, as confirmed by the low standard deviation Considering $\overline{PCT}$ as the ratio between the volume and the flow through the pulmonary circulation per unit of time (the heart cycle in our case), its constancy can be explained by the highly significant direct correlation between PBV and SV ($b = 3\ 6$, $r = 0\ 81$, $P < 0\ 001$)

The close correlation between SV and PBV could be interpreted as a dependence of PBV on SV in the light of recent studies tending to attribute to the stroke volume an important role in the regulation of the pulmonary blood volume (12, 15, 20) According to this hypothesis the correlation of PBV with cardiac output could also result from the dependence of CO on SV

With respect to the correlation between PBV and BV, it is still uncertain whether the blood volume influences PBV directly or in an indirect way through modification of the SV, anyhow the constancy of the ratio PBV/BV observed by some authors (12, 15, 20) and in this series deserves emphasis This problem is now under study in our laboratory

The close correlation of PBV with SV could also explain the lack of correlation between PBV and age as a consequence of the poor correlation between PBV and age as a consequence of the poor correlation between SV and age

Conclusions and summary

A technique has been described for routine determinations at the bedside of blood volume, cardiac output and

pulmonary blood volume with the method of quantitative radiocardiography The instrumentation is simple and the technique is easy to perform and cau es little trouble to the patients only one injection of about 50 μC of RIHSA being needed

Thirty nine patients aged from 17 to 83 years free of cardiovascular or respiratory disorders, have been studied and the results obtained are in close agreement with previous reports Only the cardiac index showed a significant decrease with age, while the reduction of blood volume and of pulmonary blood volume was slight A close statistical correlation was found between PBV and SV and was interpreted as a dependence of PBV on SV

Acknowledgement

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Acquired Agammaglobulinaemia and Malabsorption

By

O Forssman and B Herner

Cases of combined malabsorption and extreme hypogammaglobulinaemia hereinafter in accordance with normal usage called agammaglobulinaemia, have been reported by several workers (2, 4, 6, 13—14, 22, 24—27, 32—33), who have postulated causal relationship that fall into three groups

1 The mucosal lesions are primary and give rise to defective absorption of gammaglobulin or to its escape into the bowel
2 The gammaglobulin deficiency somehow gives rise to atrophy of the gastrointestinal mucosa and hence to malabsorption
3 Agammaglobulinaemia and malabsorption are due to the same inherited defect

Hypogammaglobulinaemia may be a part of serum protein alterations in primary malabsorption A quite different serum protein pattern was however, noted in the cases to be described and accordingly there is no reason to assume a causal relationship described under point 1 above

Submitted for publication July 2 1964

Case reports

Case 1 The patient was a woman born in 1921 There was no known hypersusceptibility to infection in the family During previous years she used to be troubled by a few upper respiratory tract infections each year

At the age of 39 the patient began to have bouts of frequent diarrhoea occasionally with mucus never with blood in the stools The faeces varied in consistency from one attack to another After therapy the patient's indigestion has lately been very much better

About two months after the first episode of diarrhoea the patient became excessively susceptible to infections in the form of frequently recurring attacks of pneumonia and bronchopneumonia

On numerous occasions during the past three years the patient has been treated in Borås Hospital and also for three months two and a half years ago in the Endocrine Section of the Metabolic Ward Sahlgrenska Sjukhuset Gothenburg The presence of malabsorption was definitely established since the signs varied from one occasion to the next absolute values will not be specified and only basic observations made during periods of exacerbation will be described

1 Vitamin B_{12} and folic acid deficiency in serum megaloblastic anaemia abnormal Schilling's test and folic acid clearance

TABLE I Case 1 Paper electrophoresis of serum Values in mg/100 ml

Total proteins	Albumin	α 1	α 2	β 1	β 2	γ
Patient during exacerbation of symptoms						
5 0	3 7	0 29	0 47	0 32	0 16	0 06
Patient during freedom from symptoms						
6 8	4 36	0 68	0 88	0 45	0 32	0 12
Normal range ($\overline{x}$ ± 2 S)						
6 4–7 8	4 2–5 3	0 23–0 38	0 34–0 59	0 39–0 62	0 24–0 42	0 65–1 10

2 Fat losses in faeces, varying between 100 and 21 g in 4 days
3 Subnormal values for *d* xylose test and abnormally flat glucose tolerance curve
4 Negative calcium, potassium and phosphorus balances
5 Typical flocculation picture on X ray of small bowel
6 Pathological changes in biopsy specimens of duodenal mucosa taken 85, 80 and 70 cm from the front teeth, the specimens including both mucous membrane and muscularis *mucosae No villous fringing and merely vestigial mucosal villi in the* most proximal of the three specimens The proper mucous membrane is lose and diffusely invaded by lymphocytes, plasmocytes and occasional eosinophilic leukocytes The surface epithelium exhibits cytoplasmic *vacuolization, pyknosis and displacement of the nucleus from its* normal position Here and there, moreover, the epithelium is flatter cubical rather than cylindrical Conclusion Changes as those in idiopathic sprue

Other organs

During the patient s numerous respiratory tract infections X ray examination *disclosed* bronchopneumonia and pneumonia at varying sites X ray of the mediastinum revealed no abnormalities, no dislocation or compression of the oesophagus, as might be the case in thymoma

Normal serum creatinine but low creati*nine and inulin clearance — 60 and 48 ml/* min respectively — and para amino hippuric acid clearance 280 ml/min No urinary pro*tein leakage occurred*

Despite sharply negative mineral balance X-ray disclosed no osteoporosis or osteomalacia Alkaline phosphatases not excessive Diminished tubular phosphate reabsorption

Serum protein studies

The patient belongs to blood group A_1 *Among the regular antibodies in the* ABO system, conventional methods failed to detect any Anti B But when the procedure was sharpened by testing three parts of patient serum on one part of 2 % suspensions of A_1 B and 0 blood corpuscles in the *cold* state and incubating for 30 min to an hour followed by *centrifugation weak to moderately strong* reactions were obtained with seven and a very doubtful reaction with one of eight B blood corpuscles tested On the other hand completely negative reactions resulted from six A_1 *and eight 0 blood corpuscles* No gamma globin and no β M precipitate appeared at immunoelectrophoresis Yet within the elec*trophoretic gammaglobulin domaine there* did appear another precipitate believed to be β A The possible presence of this fraction *was later made the object of* a penetrating immunological analysis using Ouchterlony s as well as Oudin s techniques but no β A

band could be demonstrated The anti human globulin inhibition test for immune globulins disclosed that the patient s serum continued to absorb antibodies against human immune globulin in a dilution of 1 20 but not in a dilution of 1 200 (the dilution is between 1 40 000 and 1 80 000 before normal serum loses its absorbing power)

Paper electrophoresis (C B Laurell, M D Malmo) see table I The values are substantially similar to those obtained at Borås Hospital

Sera from father and five sibs all subjectively healthy at the time were examined with the aid of paper electrophoresis The gammaglobulin fraction was rather high in a sister (1 24/100 ml) but laid within the range of normal variation in the others

Other immunological observations

1 Antistreptolysin titre less than 25 units
2 Antistaphylolysin titre less than 2 units
3 Mantoux 1 mg negative
4 Normal lymphocyte numbers in peripheral blood were found at repeated differential white cell counts The white cell count was within the normal range
5 Absence of plasma cells in three bone marrow smears
6 Attempt to demonstrate antibodies against plasma cells in the patient s serum Bone marrow from a normal subject belonging to the same blood group as the patient was divided into two equal portions About 1 ml of the patient s serum was added to one portion and a similar volume of serum from a normal subject to the other After incubation at 37 C for one hour in a humid chamber smears from each portion were found to include plasma cells Accordingly by this method no antibodies against plasma cells could be demonstrated in the patient s serum
7 Histological examination of two inguinal lymph nodes revealed preserved lymph node structure marginally consisting of preserved lymph follicles with distinct reactive centres where phagocytes and mitotic figures were seen No medullary cords

Therapy

Numerous treatments were administered gammaglobulin calcium assorted vitamin preparations antibiotics, prednisolone (with prophylactic antibiotics) etc In recent times the patient has continuously been on a gluten free diet and largely free from diarrhoea but the susceptibility to infection persists

Case 2 A woman born in 1912, died in 1962 The father died of pulmonary tuberculosis No other serious infections known in the family

Up to the age of 35 the patient exhibited no hypersusceptibility to infections but then she began having frequent upper respiratory tract infections and from age 45 the condition became worse and she had recurrent prolonged bouts of pneumonia and radiographically verified bronchiectasis X ray of the lungs in 1961 disclosed progression in the form of patchy parenchymal densities while bronchography revealed advanced bronchiectasis bilaterally

In the summer of 1961 she began having frequent episodes of diarrhoea leading to weight loss Following appropriate therapy the diarrhoea ceased in just under six months but seven months later the attacks returned and were refractory to treatment and gradually became more severe

Since 1957 the patient has been admitted several times to Varberg Hospital Signs of malabsorption were present in the form of greatly increased total fats in the faeces at repeated examinations and subnormal serum calcium levels The serum electrolytes were otherwise normal X ray examination of the stomach and transit time through the small bowel uncovered no abnormalities Among other investigations carried out during the patient s early admissions to hospital the following may be mentioned

1 White cell counts and differential lymphocyte counts were in the normal range
2 No radiographic widening of the mediastinum as might be the case in thymoma
3 Paper electrophoresis of serum yielded results varying from one occasion to

TABLE II Case 2 Paper electrophoresis of serum in the terminal phase of amyloidosis Values in mg/100 ml

Total proteins	Albumin	$\alpha 1$	$\alpha 2$	$\beta 1$	$\beta 2$	γ
Patient						
3.3	1.7	0.36	0.53	0.22	0.14	0.36
Normal range ($\bar{x} \pm 2$ S)						
6.4—7.8	4.2—5.3	0.23—0.38	0.34—0.59	0.39—0.62	0.24—0.42	0.65—1.10

another over the period 1957—1961, but corresponding reasonably well with changes in the course of the disease Generally speaking, however, there was a moderate reduction of total proteins (usually 5—6 mg/100 ml) and of albumin, an increased α_2 fraction (to 0.9—1.2 mg/100 ml), an initially normal but subsequently rather markedly elevated α_1 fraction (to approximately 0.6 mg/100 ml), a normal β fraction, and throughout a markedly reduced γ fraction (0.1—0.2 mg/100 ml)

In the autumn of 1961 the patient developed pronounced albuminuria Her condition had the characteristics of nephrosis The picture of azotaemia in due course supervened and concomitantly the serum electrolyte values were deranged The patient died in Nov 1962 under the clinical picture of suspected amyloidosis With the onset of nephrotic manifestations came a sharp reduction of both total proteins and the albumin fraction

Paper electrophoresis in the terminal phase (C B Laurell, M D, Malmo (table II) At immunological analysis the γ and β A arches were normal though both in reduced concentrations

At autopsy amyloid deposits were found in the liver, spleen and kidneys but not in the small bowel which, however, exhibited advanced postmortem changes

Case 3 A man, born 1932, died in 1959 No hypersusceptibility to infection known in the family

Admitted to a Stockholm hospital at age 12 with a diagnosis of non tropical sprue When first seen the boy was extremely emaciated and weighed only 18 kg While in hospital he had large, bulky stools

At about the same time the patient began to be troubled by recurrent respiratory tract infections Pneumonia was diagnosed on at least 25 separate occasions He also had repeated onsets of otitis and showed a tendency to develop furunculosis Furthermore, in 1955 he developed poliomyelitis leading to paresis of both legs Admitted to the Västerås Hospital in 1957 and subsequently there several times for his susceptibility to infections but, as he had no symptoms of it, nothing was done about his previous non tropical sprue Noteworthy signs included the following

1 The white cell count and differential lymphocyte count were in the normal range
2 Not a single plasma cell could be demonstrated in a cell rich sternal marrow specimen in 1957
3 The glucose level of fasting blood was low and the glucose tolerance curve flat
4 A test breakfast revealed the presence of histamine refractory achylia
5 No evidence of thymoma discovered at X ray examination of the chest
6 Antistreptolysin and antistaphylolysin titres were not elevated despite the history of numerous infections

Paper electrophoresis of serum was done periodically from 1957 through Sept 1958 and showed normal or slightly subnormal total protein and albumin values normal

α and β fractions and very low γ globulins (0 1—0 2 mg/100 ml)

A gastric disorder supervened in April 1959 This later proved to be gastric carcinoma which was treated surgically The patient died in a postoperative complication

Case 4 A man born in 1930 died in 1959 No member of the family known to be abnormally susceptible to infections Previously the patient s health had on the whole been good

A very high susceptibility to infections began when the patient was 21 and during the remaining years of his life he was admitted to two different hospitals about 30 times for pneumonia bronchopneumonia or bronchiectasis

At roughly the same time as these manifestations commenced the patient began to have diarrhoea and lost much weight

The more noteworthy signs were as follows

1 Normal white cell counts normal or subnormal lymphocyte proportions at differential counts
2 Megaloblastic anaemia (predominantly so-called intermediate forms of megaloblasts) low serum calcium excessive amounts of total fats in faeces
3 Abnormal levels of total serum protein and its fractions The values registered varied rather widely Total proteins were most often subnormal (4 15—6 3 mg/100 ml) the albumin fraction varied between subnormal and normal values α and β globulins were as a rule but not always moderately low, and the γ globulin fractions was conspicuously low with values between 0 06 and 0 24 mg/100 ml
4 No plasma cells could be demonstrated at repeated sternal marrow biopsies
5 No evidence suggesting the presence of a thymoma could be discovered in chest roentgenograms

All attempts at treatment including gluten free diet were of no avail and the patient s condition gradually became worse He died in Sept 1959 in a state of cachexia with large volumes of sputum Emphysema bronchopneumonia chronic bronchitis bronchiectasis enlarged omental lymph nodes enlarged spleen (weighing 370 g) presenting the picture of acute and chronic splenic infection, thin adrenals poor in lipids and mucosal atrophy in the distal portions of the mucosal atrophy in the distal portions of the small bowel were found at autopsy Microscopical examination revealed patches of hydropic degeneration in the pancreas mild atrophy of liver cell trabeculae and large amounts of lipofuchsin in the liver cells

Discussion

While all four patients exhibited normal or subnormal serum albumin level , the most conspicuous protein alteration was a great lowering of the serum γ globulin fraction The other globulin components were changed little if at all Occasionally α_1 and α_2 might even be elevated, indicating an active process (though the picture of intercurrent amyloidosis upset the terminal protein spectrum in case 2) Judging by objective criteria the gastro intestinal disturbances were due to malabsorption The crux of the matter now is whether — in conformity with the somewhat incorrect terminology intentionally used by Good et al (9) — the cases reported here can actually be classified as acquired agammaglobulinaemia For a combination of agammaglobulinaemia and malabsorption has been described so often (2, 4 6 13—14, 22 24—27 32—33) that their association cannot be ascribed to pure coincidence (e g 12) Explanations of this phenomenon have diverged as to whether agammaglobulinaemia is primary due to malabsorption (13 22 etc) or if the two are somehow connected genetically (31) Moreover it has been postulated that malabsorption at least in some cases may be a significant factor in the

TABLE II Case 2 Paper electrophoresis of serum in the terminal phase of amyloidosis Values in mg/100 ml

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Patient						
3 3	1 7	0 36	0 53	0 22	0 14	0 36
Normal range ($\overline{x} \pm 2$ S)						
6 4—7 8	4 2—5 3	0 23—0 38	0 34—0 59	0 39—0 62	0 24—0 42	0 65—1 10

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Paper electrophoresis of serum was done periodically from 1957 through Sept 1958 and showed normal or slightly subnormal total protein and albumin values normal

As in other cases of acquired agammaglobulinaemia, the age at onset in our cases (including Nos 2, 3, 4) was rather high The disease may have been clinically latent earlier (3, 17) An unknown precipitating factor may have come into action at an adult age In this context it is interesting to consider what part the thymus might have played Good's (7) first report of acquired agammaglobulinaemia combined with tumour of the thymus has been followed by further accounts by him and by other workers (5—6, 8 15—16, 18, 23, 28) In cases 2 3 and 4, in all of which the patient died, no specific study of the thymus was made at autopsy, but in all four cases there was no roentgenographic or other evidence of thymoma How thymoma can be a factor in the aetiology of agammaglobulinaemia is not understood but in animal experiments the thymus itself has been shown to play an important part in various immunological conditions (for review, see 20)

In case 2 it is reasonable to assume that the amyloidosis supervening in the terminal phase was secondary to a long pre existing chronic infection One should not unreservedly characterize the case as acquired agammaglobulinaemia The pronounced γ globulin decrease nevertheless suggests that the function of the γ globulin producing cells was defective This function conceivably underwent changes in the terminal phase of the disease when despite protein leakage due to amyloidosis the γ globulin fraction actually rose and immunoelectrophoresis (not done previously) showed normal γ and $\beta_2 A$ arches, although both in lower concentrations There exist other explanations, however, for the not uncommon combination of agammaglobulinaemia and secondary amyloidosis (19)

In case 3 the patient died at the early age of 27 following an operation for gastric carcinoma It has been pointed out that familial occurrence of mesenchymal diseases — a point not studied in this case — and of agammaglobulinaemia is a combination with room for a third factor namely malignancies (31) The patient's prolonged gastrointestinal disorder could, however, itself have been predisposing to the development of gastric carcinoma

Summary

Four cases of presumed primary acquired agammaglobulinaemia combined with malabsorption are reported The causal relationship between these two conditions can be discussed with greater precision only on the basis of special studies of the patient's immunological status, including such things as immunoelectrophoresis and titres of any isoagglutinins against heterologous blood groups or absence of plasma cells in the bone marrow Case 1 satisfied these criteria for acquired agammaglobulinaemia suggesting that the malabsorption was secondary to or genetically concomitant with the agammaglobulinaemia Binding proof of such a diagnosis was missing in the three remaining cases but two of them exhibited other interesting features Thus one of the patients developed a terminal amyloidosis in spite of the fact that at least in early stages the function of the

aetiology of acquired agammaglobulinaemia (12)

In this respect the electrophoretic pattern is of great significance for the right interpretation In established cases of primary malabsorption the albumin decrease is dominant (1, 21), though not invariably (12), and to a lesser extent the other protein fractions *also* decrease (3, 4) The γ globulin, however, may occasionally remain normal or rise slightly (1, 12) But in the series of 20 cases studied electrophoretically by Huizenga et al (12) all had decreased serum albumin and 6 had lowered γ globulin (range 0 27—0 74 mg/100 ml versus 0 9—1 4 mg/100 ml in controls) while their other globulin fractions were normal This γ globulin reduction was thus relatively moderate, differing clearly and without overlapping from the considerably lower values noted in cases where acquired primary agammaglobulinaemia — even combined with malabsorption — has been established on other indications Though paper electrophoresis admittedly yields too high globulin values (31), conventional electrophoretic methods in proven cases of this disease constellation — perhaps borne out by immunoelectrophoretically demonstrated complete absence of immune globulins — yield γ globulin values lying in the range 0—0 16 mg/100 ml (2, 4, 6, 13—14, 22, 24—27 32—33) Even greater value for classification of the cases must of course be ascribed to other diagnostic criteria, such as absence of heterologous blood group antigens, complete or almost complete absence in immunoelectrophoretic studies of all the three immune globulins, absence of plasma cells in the haematopoetic tissues, etc — Finally, the possibility of protein-losing enteropathy should be considered In this event the globulin fraction may, though not often, accompany the protein leakage into the gastrointestinal tract (11, 29, 30) Clearly this mechanism was not at work in our four cases

Against this background, it seems clear that the agammaglobulinaemia in case 1 was acquired and the malabsorption secondary or concomitant This is emphasized by the fact that the γ globulin fraction was not significantly altered during the prolonged period when the patient was on a gluten free diet and had no symptoms of indigestion, even if the malabsorption *could* have been clinically latent at the time (10) An analogous case has been reported in which the γ globulin rose to 0 28 mg/100 ml during a period of subjective freedom from symptoms (12) The reason for the difference between this case and ours is probably because even if the immunological defect, and hence the loss of γ globulin producing capacity, is severe in acquired agammaglobulinaemia, it may exhibit different degrees of severity (8, 9)

Conclusive proof is lacking that cases 2, 3 and 4 also deserve the designation of acquired agammaglobulinaemia But the very pronounced decrease of the γ globulin fraction, as a rule to between 0 1 and 0 2 mg/100 ml, with the other globulin fractions substantially normal, deviates sharply from the electrophoretic pattern in malabsorption Furthermore no plasma cells could be demonstrated in bone marrow smears in cases 3 and 4

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The Normal Passage of Serum-albumin into the Gastro-intestinal Tract and its Role in the Catabolism of Albumin

An Experimental Study in Dogs

By

JARL WETTERFORS

A leakage of serum albumin into the gastro-intestinal tract has been shown to occur normally (2, 11 13) Quantitative aspects of this leakage in man were dealt with by Wetterfors et al in 1960 (24) *Albumin* catabolism seems to occur *mainly* in the stomach and the upper part of the intestine This leakage has been further established in investigations on animals (1 4 9 26)

In order to obtain more detailed data *on the* magnitude of the normal leakage *in* the different parts of the gastro-intestinal tract and on its importance in albumin catabolism the *following in*vestigation was *performed* in *dogs* by means of *homologous* ^{131}I albumin and using a non traumatic perfusion technique

Material and methods

Twenty three adult healthy *mongrel dogs* weighing 10–25 kg were used They were all in good nutritional *condition* with no signs of gastro-intestinal disorders Intravascular albumin and plasma volumes of the dogs studied metabolically (except dog *no 38*) are given in table I Some of them were kept in a metabolic cage where urine and faeces could be collected separately The dogs were not studied in *order of number* as *other* experiments were carried out simultaneously

^{131}I albumin and albumin

For reasons published elsewhere (*27*) it was judged necessary to use homologous albumin This was produced by *zone-electro*phoresis of canine plasma *in* polyvinyl-*chloride* The albumin fraction was collected *dialyzed* and freeze-dried Labelling of the albumin with ^{131}I was performed by McFarlane s technique (17) The labelled *product* contained less than 1 % *of non proteinbound* radioactivity

The intravenously administered doses varied between 30 and 150 μC The injection was performed under light Nembutal *anaes*thesia (~ 30 mg/kg body weight) The activity of the 9 *minute* sample or in some animals the average for the 9 and 12 min

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globulin producing cells must have been defective, and the second patient died of gastric carcinoma at the early age of 27

Acknowledgement

The authors are indebted to P Wising M D Vasterås Hospital, Vasteras for kindness in allowing publication of case 3

Addendum

During the course of printing this paper *G E Allen* and *D R Hadden* (Brit Med. J *2* 486 1964) have reported two brothers 25 and 27 years of age with congenital hypogammaglobulinemia associated with steatorrhea Both cases responded to parenteral gammaglobulin replacement but not to a gluten free regimen *A genetic model of a possible inheritance pattern* was constructed

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From K n Gus af V s Research Inst tute (Head G B ke M D) and the Surg cal D partment (Head J Adams Ray M D) Karol nska Sjukhuset Stockholm S eden

The Normal Passage of Serum albumin into the Gastro intestinal Tract and its Role in the Catabolism of Albumin

An Experimental Study in Dogs

By

JARL WETTERFORS

A leakage of serum album n into the gastro- ntest nal tract has been shown to occur normally (2 11 13) Quanti ta e a pects of th s leakage *in man* were dealt w th by Wetterfors et al n 1960 24) Album n catabol sm seems to occu ma nly n the stomach and the upper part of the intest ne Th is leakage has been further establ hed n invest gat ons on an mals (1 4 9 26)

In order to obta n more deta led data on the magn tude of the normal leakage n the d fferent parts of the gastro- n te nal tract and on its mportance in album n catabol sm the follow ng in ves gat on was performed in dogs by means of homologous [131]I album n and u ng a non traumat c perfus on tech n que

Material and methods

Twen y three adult heal hy mongrel dogs we ghing 10—25 kg were used They were all n good nutrit onal cond t on with no s gns of gastro- ntes nal d so ders Intra vascular albumin and plasma volumes of the dogs stud ed metabol cally except dog no 38 are g en n table I Some of them ere kep n a metabol c cage where urine and faeces could be collected separa ely The dogs were not s ud ed n order of number as o her expe ments ere carr ed out s mul taneously

[131]I album n and albumin

For reasons publ shed else here 27) t was judged necessary to use homologous albu m n This as produ ed by zo e-electro- pho esis of an ne plasma n polyv nyl chlo de The album n fract on as collected d alyzed and f eeze-dried Label ng of the album n w th [131]I as performed by M Far lane s techn que 17 The labelled product con a ned less than 1 % of non pro e nbound rad oac ty

The n a enously adm nis ered doses va ried be ween 30 and 150 μC The injec on was performed under l gh Nembutal anaes- hes a 30 mg/kg body we ght The ac y of the 0 m nu e sample or n some an mals the a erage fo the 9- and 12 m n

S bm ed f r pub ca on May 29 1964

TABLE I Intravascular albumin and plasma volumes in the perfused dogs The figures for kg body weight are also given as mean ± S E M

Dog	Albumin (g/100 ml)	Intravascular albumin (g)	Intravascular albumin (g/kg b w)	Plasma volume (ml)	Plasma volume (ml/kg b w)
2	2 79	12 3	1 23	441	44 1
4	3 28	24 2	2 30	738	70 3
5	2 69	11 1	1 05	412	38 9
6	2 80	19 2	1 54	688	55 0
8	2 79	13 7	1 09	490	39 0
9	—	—	—	530	46 1
14	3 81	40 6	2 03	1,068	53 4
15	3 07	20 4	1 61	663	52 1
17	2 73	18 6	1 49	682	54 6
21	3 49	39 3	1 97	1 125	56 3
22	3 80	22 0	2 10	579	55 1
26	3 55	28 0	2 07	790	58 5
29	3 56	31 8	1 85	895	52 0
34	4 54	51 7	2 58	1 140	57 0
Mean ± S E M	3 30±0 16	—	1 76±0 13	—	52 31±2 20

ute samples was taken for determination of the plasma volume Before the injection of the label the thyroid was blocked by adding sodium iodide to the drinking-water for 2 days

On plasma and on gastric and intestinal juices (perfusates) paper electrophoresis was *performed in veronal or veronal acetate buffer (ph 8 6, ionic strength 0 1 m 150 v 1—1 3 mA)* The paper strips were stained with bromphenol blue or amido black After registration of the density of the peaks on an Analytrol Spinco, the strips were cut according to the diagram obtained Quantitative readings of the albumin content (in plasma) were taken after elution of the dye by measuring the concentration of the eluted dye in a photometer at 630 mμ

Surgery and perfusions

The gastric and intestinal perfusions were made 0—9 days after the intravenous administration of the ^{131}I albumin

For 24 hours before the experiments the dogs were allowed water but no food They were anaesthetized with Nembutal intravenously (30 mg/kg body-weight) supplemented with $N_2O + O$ through an endotracheal tube Under strict surgical precautions, midline laparotomy was performed *Any bleeding was checked Very carefully the segments of the gastro-intestinal tract to* be perfused were identified the duodenum jejunum and *ileum*, the ileum denotes here the distal 3/5 of the small intestine and is thus not to be taken in its strict anatomical sense Care was taken not to grasp or even touch these segments The length of the segments to be perfused varied between 30 and 100 cm for the jejunum and ileum and 15 and 40 cm for the duodenum At the ends of the segments small incisions were made antimesenterically and Foley catheters (no 14 with 5 ml bags) introduced ~ 4 *cm and fixed by a suture everting the mu*cosa The bags were filled to occlude, but not to distend *the intestine In order to*

avoid traumatization of the upper part of the duodenum the proximal catheter in the duodenum was introduced through a gastrotomy and the bag was filled to occlude the duodenal bulb

In the gastric perfusions the stomach was occluded distally by a Foley catheter introduced via the duodenum and the bag filled just proximal to the pylorus During perfusion light traction was exerted on the catheter The perfusion was made through an oesophageal tube

Instead of filling the intestinal segments with the perfusion fluid it seemed more physiological to imitate normal conditions by perfusing continuously in the isoperistaltic direction using a standard aggregate for intravenous infusion After rinsing with isotonic saline perfusion was begun Distension of the segment was avoided

In 9 dogs the duodenum jejunum and ileum were simultaneously perfused and in 4 other dogs the jejunum alone was perfused

During perfusions the abdominal cavity was kept closed After the experiments the length of the segments was measured more exactly and the whole intestine and its different diameters were measured

The perfusion fluid contained 100 mg of trypsin inhibitor (Ovomucoid Sigma Chem Co) in 300 ml of isotonic saline (0 033 g 100 ml) This mixture was allowed to pass through the actual segment twice in 1—1 5 hours

This trypsin inhibitor was used for two reasons It does not change the pH as does acid buffer Its electrophoretic behaviour is quite different from that of serum albumin (fig 3) and thus does not invalidate the identification of albumin Checking by incubation at 37 C for 24 hours was made to assure that free ¹³¹I did not adhere to the ovomucoid

In 3 dogs (nos 21 34 38) the stomach was perfused with phosphate buffer (pH 7 2 ion strength 0 2) pH indicator paper was used to make sure that the solution did not become acid

To estimate the proteolytic capacity of different parts of the intestine 0 6—1 μC ¹³¹I albumin plus carrier albumin was added to the perfusion fluid in 3 dogs (nos 10 11 16) which had not received ¹³¹I albumin intravenously In 2 of them the duodenum jejunum and ileum were investigated in the third one the latter two parts only

In 2 dogs (nos 33 35) the occasional tendency of ¹³¹I iodide to become attached to high molecular substances in gastric and intestinal juices was investigated The perfusion fluid was the same as in the other experiments but in the stomach isotonic saline was used as well

In one dog (no 13) the influence of ordinary surgical techniques on the leakage was studied as was the effect of keeping the abdomen open during perfusion

It seemed necessary to ascertain whether the type of surgery and perfusion used here influenced the exponential part of the initial slope of the plasma activity curve or caused any change in the leakage when repeated For this purpose 2 dogs were submitted to a 4 hour anaesthesia and surgery as described one without and the other one with perfusion In a third dog the plasma activity was followed for some days after perfusion

In 7 dogs repeated perfusions were performed in one (no 22) for two consecutive hours in the others (nos 2 4 6 8 14 and 17) after an interval of 24—48 hours with or without the distal occlusion left in place (table III)

Pathological anatomical investigation

Autopsy was performed on all perfused dogs Especially the digestive tract was carefully examined macroscopically Parts of perfused as well as non perfused intestine were fixed in 10 % formalin or Helly s fluid After haematoxylin-eosin staining of the paraffin-embedded material histological examination was made

Treatment of samples

The radioactivity of the samples was measured in a well crystal scintillation detector coupled to either a Tracerlab SC-18 A Superscaler or a Versamatic II Scaler Spectrometer Both were fitted with auto-

TABLE I Intravascular albumin and plasma volumes in the perfused dogs. The figures for kg body weight are also given as mean ± S.E.M.

Dog	Albumin (g/100 ml)	Intravascular albumin (g)	Intravascular albumin (g/kg b.w.)	Plasma volume (ml)	Plasma volume (ml/kg b.w.)
2	2.79	12.3	1.23	441	44.1
4	3.28	24.2	2.30	738	70.3
5	2.69	11.1	1.05	412	38.9
6	2.80	19.2	1.54	688	55.0
8	2.79	13.7	1.09	490	39.0
9	—	—	—	530	46.1
14	3.81	40.6	2.03	1,068	53.4
15	3.07	20.4	1.61	663	52.1
17	2.73	18.6	1.49	682	54.6
21	3.49	39.3	1.97	1,125	56.3
22	3.80	22.0	2.10	579	55.1
26	3.55	28.0	2.07	790	58.5
29	3.56	31.8	1.85	895	52.0
34	4.54	51.7	2.58	1,140	57.0
Mean ± S.E.M.	3.30±0.16	—	1.76±0.13	—	52.31±2.20

ute samples was taken for determination of the plasma volume. Before the injection of the label the thyroid was blocked by adding sodium iodide to the drinking water for 2 days.

On plasma and on gastric and intestinal juices (perfusates) paper electrophoresis was *performed* in veronal or veronal acetate buffer (ph 8.6, ionic strength 0.1 m, 150 v, 1—1.3 mA). The paper strips were stained with bromphenol blue or amido black. After registration of the density of the peaks on an Analytrol Spinco, the strips were cut according to the diagram obtained. Quantitative readings of the albumin content (in plasma) were taken after elution of the dye by measuring the concentration of the eluted dye in a photometer at 630 $m\mu$.

Surgery and perfusions

The gastric and intestinal perfusions were made 0—9 days after the intravenous administration of the ^{131}I albumin.

For 24 hours before the experiments the dogs were allowed water but no food. They were anaesthetized with Nembutal intravenously (30 mg/kg body weight) supplemented with $N_2O + O_2$ through an endotracheal tube. Under strict surgical precautions, midline laparotomy was performed. Any bleeding was checked. Very carefully the segments of the gastro intestinal tract to be perfused were identified, the duodenum, *jejunum and ileum, the ileum denotes here* the distal 3/5 of the small intestine and is thus not to be taken in its strict anatomical sense. Care was taken not to grasp or even touch these segments. The length of the segments to be perfused varied between 30 and 100 cm for the jejunum and ileum and 15 and 40 cm for the duodenum. At the ends of the segments small incisions were made antimesenterically and Foley catheters (no. 14 with 5 ml bags) introduced ~ 4 cm and fixed by a suture everting the mucosa. The bags were filled to occlude but not to distend, the intestine. In order to

III) These results suggest that the technique used had only an insignificant influence on the permeability factor, and that small changes occurred only in the post operative period

Macro- and microscopical examination of the mucosa

Macroscopically no changes were detected in the perfused segments when compared with the non perfused ones (except in dog no 13)

No differences were seen microscopically (S Rubarth, M D R Veterinary College Stockholm) between perfused and non perfused intestine Nowhere could any deviation from the normal appearance be detected

In one of the dogs the duodenum (perfused and non perfused) showed a microscopical epithelial necrosis with hyalinization of the subjacent connective tissue (fibrinoid degeneration) These changes probably represent an acute peptic ulcer

Protein bound activity in perfusates

In the intestinal perfusates the protein bound fraction of radioactivity on an average corresponded to a quarter or more of the total activity The error of the method of precipitation was $\pm$ 10 % of the mean The figures were (mean $\pm$ S E M)

Duodenum 28 9 $\pm$ 6 4 % (n = 9)
Jejunum 29 1 $\pm$ 5 9 % (n = 13)
Ileum 24 5 $\pm$ 6 4 % (n = 9)

In the dog the ^{131}I iodide fraction (precipitable with $AgNO_3$) as well as the non precipitable fraction varied within a wide range (10—70 % and 5—67 % of the total activity respectively)

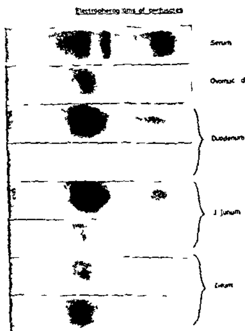


Fig 3 Paper electropherograms of ultrafiltrated intestinal perfusates from 2 of the dogs The upper two strips show electropherograms of canine serum and ovomucoid (trypsin inhibitor)

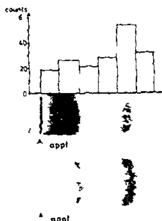


Fig 4 Electropherogram of ultrafiltrated jejunal perfusate with reference strip of serum from dog no 5 Maximum radioactivity is in the albumin area

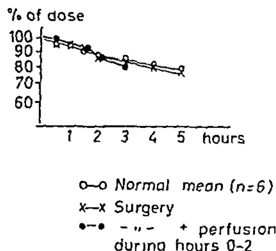


Fig 1 The initial disappearance of ^{131}I albumin from plasma (Σ of capillary transfer and catabolic rates) normally and during the surgical performance without and with perfusion

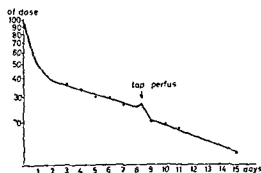


Fig 2 Semilog plot of the plasma activity before and after laparotomy with intestinal perfusion (dog no 2) Post operatively on the day of surgery there is a fall of activity but later the increase of the slope is quite small

matic sample changers All perfusates were centrifuged and the sediments examined microscopically for the presence of blood The radioactivity was measured on 2 or 4 ml samples After addition of carrier albumin and potassium iodide precipitation was done with an equal volume of 20 % trichloracetic acid (TCA), subsequently with 5 % phosphotungstic acid (PWA) and finally with 10 % $AgNO_3$ The radioactivity of the different precipitates was measured Thus the total amount leaked out protein bound activity (TCA + PWA activity) could be determined In 8 duplicate tests the error of the method of precipitation was estimated

In 8 experiments with ^{131}I albumin (6 intestinal, 2 gastric) and in one with ^{131}I iodide (1 intestinal, 1 gastric) the different perfusates were concentrated by ultrafiltration through a collodion membrane and electrophoresis was carried out The strips were cut and the radioactivity was measured in the different fractions in 4 of the albumin experiments (3 intestinal 1 gastric) and in the iodide experiment

The leakage of albumin is expressed as *ml of plasma delivering its albumin to the* gastro-intestinal tract per unit time This way is chosen because it makes treatment of *the data easier and more uniform* Thus the values determined are not dependent on the albumin concentration, but are correlated to the percentage value of catabolism expressed as a fraction of the plasma volume The ratio

$$\frac{\text{protein bound activity in perfusate}}{\text{mean activity per ml of plasma}}$$

gives a measure of the leakage in ml of plasma This is expressed per 10 cm of intestine per hour The figures will then be more easily handled

Results

Catabolic rate following surgery

The surgical procedure and the anaesthesia did not cause any change in the initial slope of the plasma activity curve (fig 1) A slight fall was observed post operatively on the day of surgery During the next 4—5 post-operative days there was a slight increase of the slope as compared to the pre operative period indicating a post operative change of the catabolic rate or/and the capillary transfer rates (fig 2) With two exceptions no increase in the leakage could be demonstrated in any of the dogs in which repeated perfusions were made after different intervals of time (table

The individual values are corrected with the factor $\frac{100}{62\ 8}$, while the mean $\pm$ S E M are corrected with $\frac{100}{62\ 8 \pm 3\ 9}$ It will be seen that the maximal leakage occurs in the duodenum with 0 218 $\pm$ 0 023 *ml* per *10* cm and hour, followed by the jejunum with 0 102 $\pm$ 0 018 ml per 10 cm and hour, while it is smallest in the ileum with 0 063 $\pm$ 0 014 ml per 10 cm and hour The colon is not taken into consideration In those 8 dogs in which comparison between the different parts could be made, the differences between uncorrected values were significant ($0\ 01 > p > 0\ 001$) With correction for the proteolytic factor, the significance of the difference between the duodenum and the jejunum decrea ed ($0\ 02 > p > 0\ 01$), otherwise the significance levels were unchanged

In the stomach the leakage was 0 17 0 36 and 1 14 ml of plasma per hour in the three investigated dogs

In dog no 13 in which an ordinary surgical technique was used and the ab domen was left open during perfusion very high values for the leakage were found (table *II*)

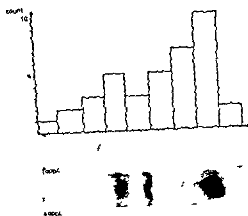


Fig 6 Electropherogram of ultrafiltrated gastric perfusate (dog no 34) compared with serum Maximum radioactivity is over the albumin area

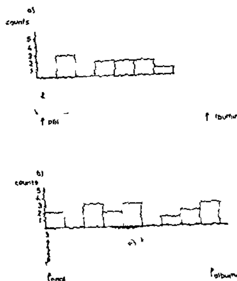


Fig 7 After administration of ¹³¹I iodide intra venously dog no 34) no radioactivity is found in the ultrafiltrated gastric perfusate a nor in the intestinal perfusate b)

The gastro-intestinal leakage of albumin correlated to the degradation

The normal catabolism of albumin in dogs is 17 7 $\pm$ 0 38 % of the intravascular pool measured by means of homologous ¹³¹I albumin (27) As no deviations from this pattern could be demonstrated in consequence of surgery this value is valid in the following estimation As it has been empirically well established that albumin is catabolized in the intravascular pool or its immediate vicinity the degradation may also be expressed as that fraction of the plasma volume which per 24 hours delivers its albumin for catabolism i e 17 7 %

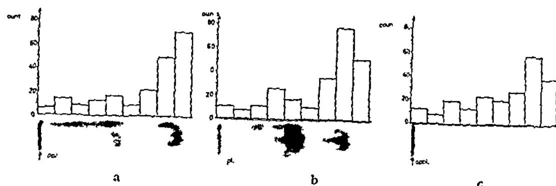


Fig 5 Electropherograms (dog no 8) of ultrafiltrated perfusates from the duodenum (a) jejunum (b) and ileum (c) Maximum of radioactivity is in the albumin area

In the three gastric perfusates the TCA—PWA precipitable fraction constituted 1 3 % 3 0 % and 7 3 % of the total activity

Identification of albumin

The TCA precipitates were soluble in 95 % ethanol a specific characteristic of the TCA albumin (16)

Electropherograms of the ultrafiltrates *are shown in fig 3 together with plasma* and ovomucoid They show exclusively a fraction with the same mobility as serum albumin Maximum radioactivity is located in this area (figs 4 and 5) In the gastric juice the findings were the same (fig 6) After administration *of ¹³¹I iodide electrophoresis of gastric* and intestinal juice *showed albumin* but no significant activity on the strips (fig 7)

Proteolytic activity in the intestine

The proteolytic activity related to ¹³¹I albumin was fairly uniform in the different parts of the intestine About 40 % of the label perfused was degraded in 1 hour i e 62 8 ± 3 9 % (mean ± S E M n = 8) of the activity in the perfusates was still precipitable with TCA + PWA This means that a correcting factor of $\frac{100}{62\,8 \pm 3\,9}$ had to be used in estimating the absolute leakage of ¹³¹I albumin

Affinity of free ¹³¹I iodide for high molecular substances

After intravenous administration of ¹³¹I iodide perfusions demonstrated a very *small tendency to attachment of iodide* activity to TCA—PWA precipitable molecules in the intestinal juice Only 0 5—2 2 % of the total activity was precipitable with TCA—PWA

In the gastric juice 1 7—2 5 % of the activity was TCA—PWA precipitable *irrespective of whether buffer or saline was used indicating that a not negligible* fraction of iodide radioactivity attaches to high molecular substances Electropherograms *showed albumin* but no activity on the strips (fig 7)

Quantitation of the passage of ¹³¹I albumin into the different parts of the gastro intestinal tract

Table II shows the figures for the leakage of albumin into the duodenum jejunum and ileum uncorrected and corrected

The individual values are corrected with the factor $\frac{100}{62\ 8}$ while the mean $\pm$ S E M are corrected with $\frac{100}{62\ 8 \pm 3\ 9}$ It will be seen that the maximal leakage occurs in the duodenum with 0 218 $\pm$ 0,023 ml per 10 cm and hour followed by the jejunum with 0 102 $\pm$ 0 018 ml per 10 cm and hour, while it is smallest in the ileum with 0 063 $\pm$ 0 014 ml per 10 cm and hour The colon is not taken into consideration In those 8 dogs in which comparison between the different parts could be made, the differences between uncorrected values were significant (0 01 $> p >$ 0 001) With correction for the proteolytic factor the significance of the difference between the duodenum and the jejunum decreased (0 02 $> p >$ 0 01), otherwise the significance levels were unchanged

In the stomach the leakage was 0 17 0 56 and 1 14 ml of plasma per hour in the three investigated dogs

In dog no 13 in which an ordinary surgical technique was used and the abdomen was left open during perfusion, very high values for the leakage were found (table II)

The gastro-intestinal leakage of albumin correlated to the degradation

The normal catabolism of albumin in dogs is 17 7 $\pm$ 0 38 % of the intravascular pool measured by means of homologous ^{131}I albumin (27) As no deviations from this pattern could be demonstrated in consequence of surgery this value is valid in the following estimation As it has been empirically well established that albumin is catabolized in the intravascular pool or its immediate vicinity the degradation may also be expressed as that fraction of the plasma-volume which per 24 hours delivers its albumin for catabolism i e 17 7 %

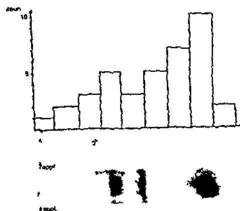


Fig 6 Electropherogram of ultrafiltrated gastric perfusate (dog no 34) compared with serum Maximum radioactivity is over the albumin area

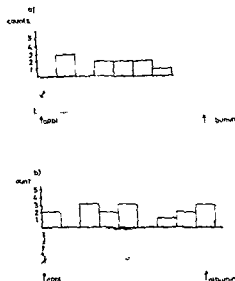


Fig 7 After administration of ^{131}I iodide intravenously (dog no 3) no radioactivity is found in the ultrafiltrated gastric perfusate a) nor in the intestinal perfusate b)

TABLE II Release of albumin from plasma into the intestine expressed as ml of plasma/10 cm/hour. The values of dog no. 13 demonstrate the effect of ordinary surgical handling and open abdomen during perfusion (the value for the ileum of dog no. 15 is excluded from the statistical calculations as this dog had a helminthiasis in the ileum)

Dog	Duodenum		Jejunum		Ileum		Days between injection of ^{131}I albumin and perfusion
	Uncorr	Corr	Uncorr	Corr	Uncorr	Corr	
2	–	–	0.050	0.080	–	–	3
4	–	–	0.102	0.162	–	–	1
5	–	–	0.032	0.052	–	–	1
6	–	–	*0.021*	*0.033*	–	–	*1*
8	0.135	0.215	0.022	0.034	0.009	0.015	3
9	0.193	0.308	0.123	0.196	0.047	0.075	0
14	0.101	0.161	0.040	0.064	0.010	0.017	0
15	0.181	0.288	0.043	0.068	0.149	–	9
17	0.096	0.153	0.124	0.198	0.043	0.069	1
21	–	–	0.045	0.072	0.021	0.033	1
22	0.115	0.183	0.107	0.171	0.068	0.108	2
	0.167	0.266	0.083	0.132	0.068	0.108	
26	0.130	0.207	0.040	0.064	0.023	0.037	0
29	0.117	0.187	–	–	0.068	0.108	0
Mean ±	0.137	0.218	0.064	0.102	0.040	0.063	–
S.E.M.	±0.012	±0.023	±0.011	±0.018	±0.008	±0.014	–
13	*0.393*	*0.626*	*0.330*	*0.526*	0.368	0.586	–

TABLE III Leakage of albumin expressed as ml of plasma per hour and 10 cm of intestine at repeated perfusions with 5–48 hour intervals with or without occlusion

Dog	Leakage by 1st perfusion (ml)	Leakage by 2nd perfusion (ml)	
2	0.050	0.031	5 hour interval with anaesthesia all the time. Occluding balloon in place
4	0.102	0.165 (a) 0.050 (b)	6 hour (a) 12 hour (b) interval with anaesthesia all the time. Occluding balloon in place
6	0.021	0.014	24 hour interval with anaesthesia all the time. Occluding balloon in place
8	0.009	0.011	48 hour interval. Perfusions of normal non-occluded intestine
14	0.040	0.033	48 hour interval. Distal occlusion
	0.010	0.043	48 hour interval. Normal intestine. No occlusion
17	0.124	0.056	48 hour interval. Distal occlusion
	0.043	0.027	48 hour interval. Normal intestine. No occlusion

TABLE IV Ro e of he sma l gut and ts h ee ma n pa n the degradat on of albumin n he dog (expressed a a per entage of the to al catabolism)

D g	[illegible]	Album n release (ml of plasma per day) n			Role of n es ne n degrada on as % of to al ca abolis n			Σ %
		Duodenum	Jejunum	Ile m	Duodenum	Jejunum	Ileum	
8	8 8	23 3	9 4	6 1	26 8	10 8	7 0	44 6
9	93 9	22 2	37 [illegible]	21 4	23 6	40 0	22 8	86 4
14	189 0	15	23 9	9 2	8 2	12 6	4 8	25 6
17	120 6	12 7	51 3	26 6	10 5	42 5	22 0	76 0
[illegible]	10 3	17 6	42 6	40 3	17 2	41 6	39 3	98 1
	10 5	25 2	32 9	40 5	24 6	32 1	39 5	96 2
[illegible]	40 0	17 4	17 2	14 8	12 4	12 3	10 6	35 3
21	199 0		2 5	18 8		13 9	9 5	23 4
9	158 5	17 8		58 4	11 2		36 8	48 0
15	117 7	24 2	16 2		20 6	13 8		34 4
[illegible]	77 0		21 1			27 1		27 1
4	130 6		1 3			39 3		39 3
	9		13 9			19 1		19 1
6	121 8		9 4			7 7		7 7
M an					17 2	24 1	21 4	62 7 66 0
S E M					2 3	±3 7	±4 8	(~ [illegible]

Tl us it is po ible to est mate tl e role played n tl e degradat on by the different parts of tl e gastro intest nal canal n each an mal as v ell as in the ser es as a hole In table IV these est m t o s are tal ulated It w ll be see f om tl o e dogs n wl cl all parts f the ntest e ere perfused that tl e leakage was respons ble for a mean of 66 26—98 f the degradat on If tl e role f tl e d fferer t parts of tl e test ne s determ ned per se one f nds tl at tl e jej n m s respon ble f r ~ f tl e leum f r ~21 % and tl e l oden m i sp te of its relat e sl ort ness for 17 % In other v ords an a er age of two th rds of tl e total catabol sm occurs in the intest nal tract

The stomach s respons ble for 2—19 % when no correct on is made for the iod de l nd ng capac ty Tak ng th s into cons derat o i less tl an 10 % of tl e catabol sm takes place n tl e stomach

Inte t nal album n leakage — intest nal surfa e

The plane surfaces of tl e duodenum je n m pr x mal [illegible] and ileum (d stal 3 5) were determ ned from meas rements of tl e lengtl and d ameter of

respective parts in each dog The leakage per unit of plane surface was thus calculated as the mean ± S E M
Duodenum 0 102 ± 0 01 ml plasma/sq cm/day
Jejunum 0 061 ± 0 01 ml plasma/sq cm/day
Ileum 0 047 ± 0 01 ml plasma/sq cm/day

Discussion

The quantitative importance of the gastro intestinal tract in the degradation of serum albumin is still debated The controversy hinges mainly on the technique used in the investigations

In man, operative studies (24) have given results indicating that the main part of the catabolism occurs in the gastro intestinal tract This has not been verified by the ion exchange technique introduced by Jeejeebhoy (14) However, much doubt has recently been cast on this method (6)

In studies on rabbits (1) it is found that the entire extrahepatic breakdown of albumin occurred in the gut The same observation is made in the sheep (4) Glenert et al (9) have stated that the leakage would be greater in the upper part of the intestine of the dog and that 1/2—2/3 of the catabolism of albumin in this species would occur in the alimentary canal Any methods involving the use of isolated intestinal loops were abandoned in this study as their capillary architecture changes rapidly (18) Attempts to construct intestinal segments which during non experimental periods were taking part in the passage of food were unsuccessful It had to be shown that the operative procedure used in this investigation was non traumatic Strong evidence for this is the unchanged slope of the initial distribution curve reflecting the sum of capillary transfer and catabolic rates during a 3—5 hour period Should the procedure be traumatic in itself a progressive increase of the leakage would occur with repeated perfusions This was not the case The small post operative increase of the slope says nothing of the behaviour at operation, but shows only that the post operative period is unsteady with a slight increase in catabolic and/or capillary transfer rates Continuous isoperistaltic perfusions without distension the intestine must be the most correct imitation of the normal physiology Ordinary surgical handling evidently increases the leakage

The identification of albumin did not involve any difficulties, as both the ethanol solubility of the TCA precipitates and electropherograms showed the identity In man this identity has been well demonstrated immuno electrophoretically (13, 24)

Furthermore maximum radioactivity was in the albumin area, in the intestinal as well as the gastric samples The absence of radioactivity on the strips in the ¹³¹I iodide experiment further stresses the authenticity of the findings The fact that radioactivity is present in other parts of the strips is not remarkable as it has been shown (15) that enzymatic degradation of albumin gives products with slower electrophoretic mobility It has also been demonstrated that in paper electrophoresis there is an irreversible adsorption of albumin all over the filter paper (19

The precipitability showed good uniformity in the different parts of the intestine, as did the determined proteolytic activity

The correction factor for proteolysis may in reality be still greater, as proteolysis probably is more intense when the substrate is evenly distributed over the mucosa than when it is introduced in a unidirectional flow from one end Determination of the proteolytic activity may sometimes be a much easier way to solve the problem of intestinal proteolysis than trying to estimate the intestinally derived iodides or iodinated amino-acids This proteolytic factor has not been taken into account in earlier investigations The non precipitable radioactivity has been considered as wholly derived from proteolysis (24) or the trypsin inhibitor used has been credited with a 100 % antiproteolytic effect (9)

The very small tendency of free ^{131}I to attach to proteins or mucinous elements did not influence the results significantly in estimating the intestinal leakage In the gastric juice however where the protein bound fraction was small this tendency may be a source of error and the estimations of the albumin leakage are here very approximate and it can only be said that the value was under 10 % In antrectomized dogs with Heidenhain pouches this attaching tendency of free ^{131}I in the gastric juice was recently pointed out by Gelb et al (8)

Leakage — intestinal surface — degradation It is shown that the duodenum has the greatest leakage per unit length as well as per sq cm plane surface Next comes the jejunum and lastly the ileum (No determination of the colonic leakage was made, as adequate cleansing of the bowel was not compatible with a non-traumatic procedure) The stomach evidently has the smallest leakage It has been postulated that the duodenum and jejunum should have the same leakage (1, 9) Evidently it is not so, in spite of the shortness of the duodenum its total leakage is of the same magnitude as that of the whole ileum

Of the normal degradation of albumin in the dog, 17 7 % of the intravascular pool, the small intestine is responsible for two-thirds and the stomach for one tenth or less Other possible sites of degradation have also been investigated Cohen and Gordon (5) and Gordon (10) have shown that ~ 15 % of the break down occurs in the liver That the kidneys are not responsible for any degradation has been documented (21) The reticuloendothelial system does not participate in the catabolism (23)

Another observation supporting the findings reported here concerns the blood flow to the intestine Geber (7) found that the intestinal blood flow was maximal in the duodenum with a gradual decrease in the distal direction Steiner and Mueller (22) showed that the blood flow through the stomach is less than in all other parts of the alimentary tract excluding the recto-sigmoid The same results were achieved by using a different technique (27)

This good correlation between the blood flow and the leakage of albumin into the different parts of gastro-intestinal tract speaks in favour of a functional correlation The following deductions may thus be made 1) The

leakage per unit *true mucosal surface* is equal throughout the whole gastro-intestinal tract. 2) Variations in blood-flow bring about proportional variations in albumin leakage, which means there exists a certain periodicity, i. e. an increase in connection with alimentation, and a decrease during rest.

The literature contains no estimations of the true mucosal surface in different parts of the intestine. But because of the distally decreasing richness in folds and villi it is evident that 1 g or 1 sq. cm of plane surface of the duodenum have a *larger true mucosal surface* than have 1 g or 1 sq. cm of plane surface of the other intestinal parts. Thus, *the first* deduction is not inconsistent and it *would further indicate that the leakage* of albumin is not so much an active secretory process as more a passive one depending on the capillary — interstitial — intraluminal rate of transfer in the different species.

As to the second deduction, it pertains to the functioning of the gastro-intestinal tract at work and at rest. Alimentation *increases the intestinal blood* flow (3, 12, 20). Thus a variety of *factors*, humoral as well as osmolar cooperate in the regulation of the blood flow and blood content of the intestine.

Several aspects of albumin leakage/blood flow remain to be studied experimentally, but the correlation pointed out may suggest a periodicity in the leakage of albumin and thus also in degradation synchronous with the functional state of the alimentary tract. Further support for this view comes from the decrease of albumin breakdown seen in starvation due to cardiac stenosis (25).

Summary

Twenty three dogs were investigated in order to determine *the leakage of al*bumin into the gastro-intestinal tract and the part played by this leakage in the degradation of albumin. Homologous ^{131}I albumin was used.

A definitely non-traumatic technique was employed which involved no effect of operation on the behaviour of albumin. The proteolytic activity of the in*testine was also investigated*, as was the tendency of ^{131}I iodide to attach to larger molecules.

When related to unit length or plane surface, the physiological leakage of albumin is greatest in the duodenum, followed by the jejunum. The intestinal leakage is smallest in the ileum. The gastric leakage plays a minor role. The colon was not *investigated*.

An average of two thirds of the normal catabolism *of albumin* occurs by the intestinal route, while the stomach accounts for one tenth or less. Altogether an average of 3/4 (range 1/3—1/1) of the catabolism occurs in the alimentary tract. A correlation between the magnitude of the leakage and the *blood flow in different parts of the* gastro-intestinal tract seems probable.

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Book review

Nobel Lectures Physiology or Medicine 1912—1962 Elsevier Publishing Company, Amsterdam London New York, 1964 838 p, 200 ill and 33 tables

"The Nobel Foundation has since 1901 each year published *Les Prix Nobel* which contains all Nobel Lectures of that year, always in the language in which they were given, as well as short biographies of the laureates In addition an account is given of the prize award ceremonies in Stockholm and in Oslo, including pre sentation addresses and after dinner speeches, etc thus covering the whole field of Nobel Prize events of one year "

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